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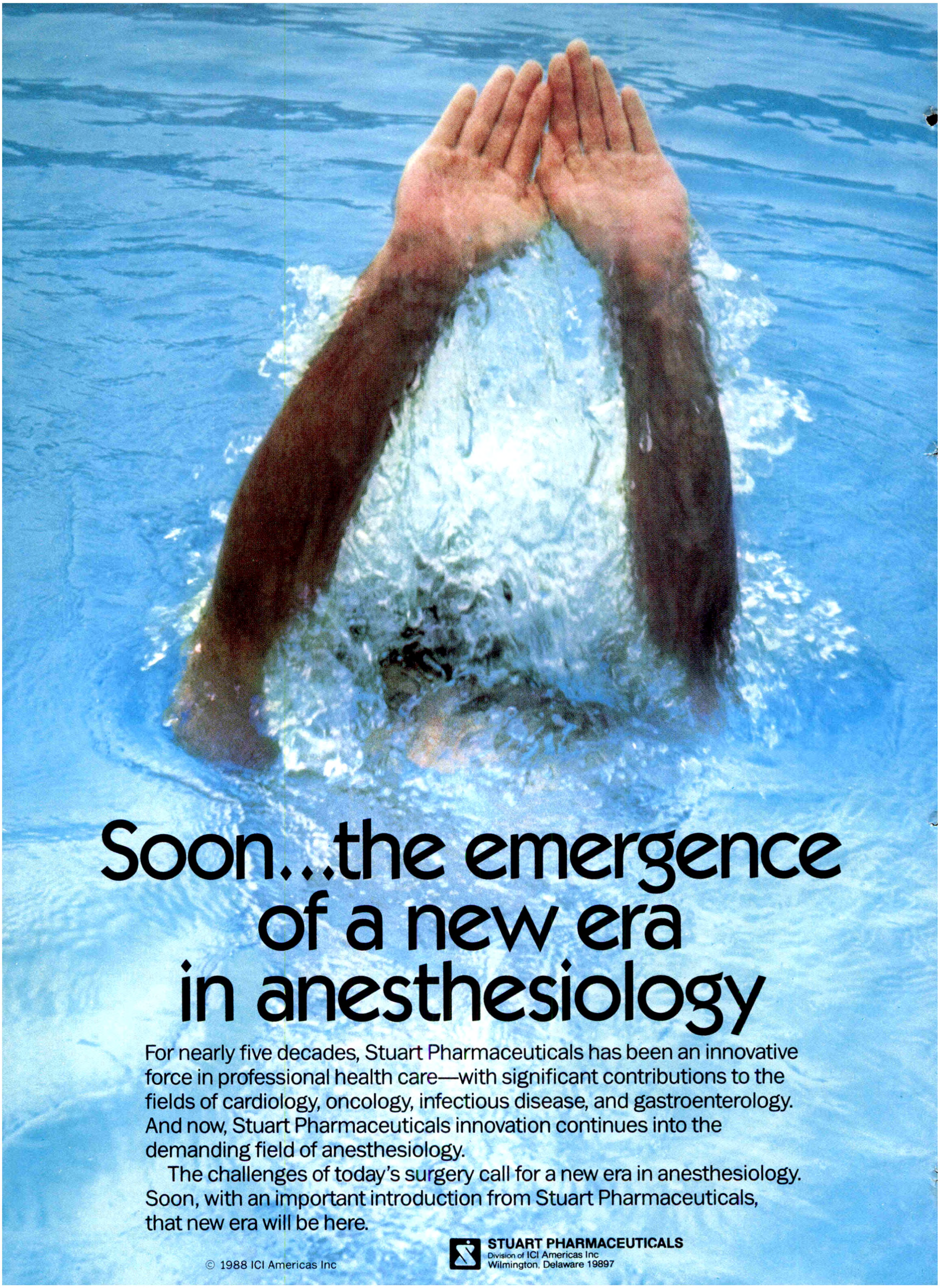

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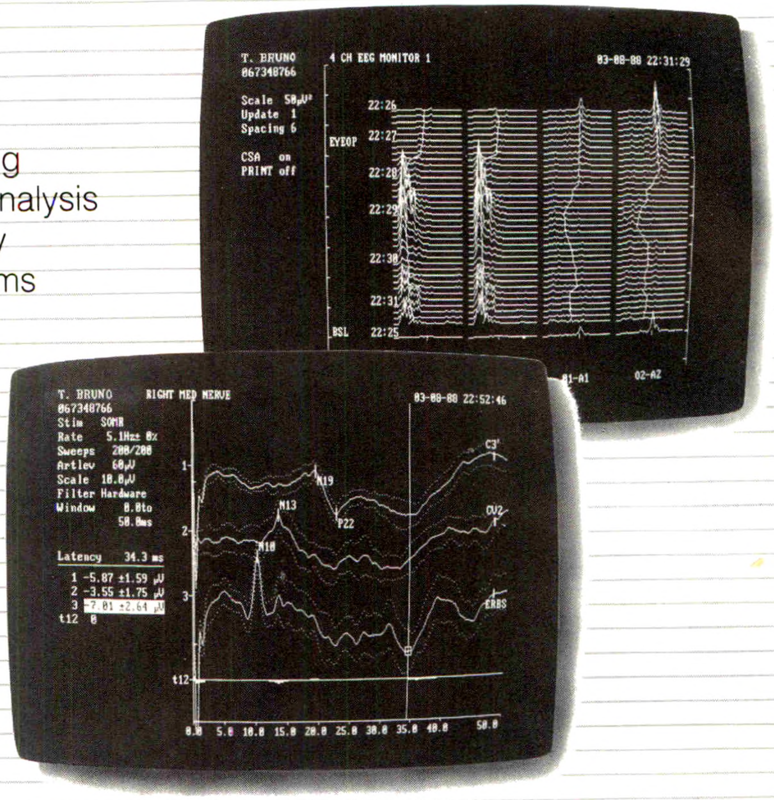

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Sufentanil Pharmacokinetics in Patients with Cirrhosis

M. Chauvin, MD, C. Ferrier, MD, J. P. Haberer, MD, C. Spielvogel, MD, C. Lebrault, MD,
J. C. Levron, PhD, and P. Duvaldestin, MD

CHAUVIN M, FERRIER C, HABERER JP, SPIELVOGEL C, LEBRAULT C, LEVRON JC, DUVALDESTIN P. Sufentanil pharmacokinetics in patients with cirrhosis. Anesth Analg 1989;68:1–4.

The effects of cirrhosis on the elimination kinetics and plasma protein binding of sufentanil were evaluated in 12 anesthetized patients with uncomplicated cirrhosis and these findings were compared with data from age-matched control anesthetized patients with normal hepatic and renal function. Sufentanil 3 μg/kg was given intravenously as a bolus injection and venous plasma concentrations were measured at intervals up to 10 hrs. The average (±SD) elimination half life was 3.5 ± 0.9 hrs in controls and did not differ in cirrhotics: 4.1 ± 0.6 hrs. The plasma clearance did not differ between the two groups: 11.3 ± 2.5 $ml \cdot min^{-1} \cdot kg^{-1}$ in controls and 10.8 ± 4.6 $ml \cdot min^{-1} \cdot kg^{-1}$ in cirrhotic patients. The sufentanil free fraction was also similar in controls (8.3 ± 1.5%) and in cirrhotic patients (9.6 ± 1.8%). These data suggest that sufentanil in a single dose should have a similar duration of action in patients with uncomplicated cirrhosis and in normal patients.

Key Words: ANALGESICS—sufentanil. PHARMACOKINETICS—sufentanil. PROTEIN, BINDING—sufentanil. LIVER, CIRRHOSIS—sufentanil.

Sufentanil, like other opioids, is extensively metabolized by the liver before its excretion as metabolites. Sufentanil undergoes oxidative N-dealkylation and O-demethylation to essentially inactive compounds (1). Owing to its hepatic elimination, it would be expected that sufentanil clearance should be decreased in cirrhosis. The aim of the present study was to evaluate the influence of cirrhosis on the pharmacokinetics and plasma protein binding of sufentanil in anesthetized patients.

Methods

Twelve patients with cirrhosis, aged 38 to 78 yr (52 ± 12, mean ± SD) and weighing 56 to 102 kg (mean 70 ± 12), and 9 patients with normal hepatic and renal function, aged 36 to 76 yr (mean 49 ± 15) and weighing between 51 and 93 kg (mean 68 ± 17) took part in the study after giving informed consent. The study was approved by the Institutional Board of Paris 5 University. Table 1 summarizes clinical features of the patients.

Cirrhosis was caused by alcoholism in all patients and had been diagnosed by a liver biopsy. At the time of the study none of the patients had ingested alcohol for at least 1 week and none had ascites, overt jaundice, or encephalopathy. Nine of the patients with cirrhosis had general anesthesia for sclerosing injections of esophageal varices, two had abdominal surgery, and one had a parotidectomy. Four of the control patients had abdominal surgery and five had orthopedic surgery. Premedication consisted of lorazepam 2.5 mg orally the night before and 2 hrs before anesthesia. Anesthesia was induced with thiopental 6 to 8 mg/kg IV; vecuronium 0.1 mg/kg was given to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen delivered by mechanical ventilation adjusted to maintain end-tidal CO_2 at 5% (Datex CO_2 analyzer). Hypothermia was prevented by heating inspired gases and use of a warming blanket.

A single bolus dose of 3 μg/kg sufentanil was given intravenously 5 min after the thiopental was administered. Venous blood samples were obtained 5, 10, 15, and 30 min and 1, 1,5, 2, 3, 4, 6, 8, and 10 hrs after administration of the sufentanil.

Sufentanil plasma concentration was determined by radioimmunoassay with a sensitivity limit of 50

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Address correspondence to Dr. Chauvin, Department d'Anesthesie et de Reanimation Chirugicale, Hopitaux de Paris, 9 Avenue Charles de Gaulle, 92104 Boulogne Cedex, Paris, France.

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Table 1. Patient Characteristics

	Sex	Age (yr)	Body weight (kg)	Operation
Controls				
1	M	61	90	Colectomy
2	M	37	52	Cholecystectomy
3	M	41	51	Vagotomy
4	M	66	93	Cholecystectomy
5	F	76	60	Hip arthroplasty
6	M	42	66	Shoulder arthroplasty
7	F	37	55	Knee ligamentoplasty
8	M	36	84	Shoulder ligamentoplasty
9	F	45	58	Hip arthroplasty
Cirrhotics				
1	M	57	75	Umbilical herniorrhaphy
2	M	53	63	Colectomy
3	M	62	72	Parotidectomy
4	F	38	65	Sclerosis of esophageal varices
5	M	38	82	Sclerosis of esophageal varices
6	M	65	79	Sclerosis of esophageal varices
7	M	52	58	Sclerosis of esophageal varices
8	M	53	102	Sclerosis of esophageal varices
9	M	61	64	Sclerosis of esophageal varices
10	M	42	65	Sclerosis of esophageal varices
11	F	38	65	Sclerosis of esophageal varices
12	F	78	56	Sclerosis of esophageal varices

Table 2. Preoperative Laboratory Data

	Prothrombin time (sec)	SGPT* (IU)	Albumin (g/L)	α1 GP† (g/L)
Controls	12.0	15	38	2.3
	12.0	12	29	0.6
	12.0	ND	43	0.8
	12.5	26	28	0.9
	13.0	15	38	0.5
	13.5	18	40	0.6
	12.5	25	37	0.5
	14.0	13	39	0.3
	12.5	24	32	0.6
Mean ± SD	13.0 ± 0.7	19 ± 6	36 ± 5	0.8 ± 0.6
Cirrhotics	16.5	37	34	0.2
	13.5	24	39	2.2
	16.5	38	29	0.5
	16	36	34	0.9
	15	13	35	2.2
	16.5	21	34	0.3
	13.5	15	41	0.6
	17	41	40	0.6
	16.5	11	44	4.1
	17	66	41	0.2
	16.5	61	20	1.2
	14	45	34	0.2
Mean ± SD	15.7 ± 1.3‡	34 ± 18	37 ± 4	1.1 ± 1.2

*Serum glutamic-pyruvic transaminase, normal value <30 IU.
†α1-acid glycoprotein, normal value >0.30 g/L <0.90 g/L.
‡$P < 0.05$ vs. controls.
Abbreviation: ND, not done.

pg/ml (2). This radioimmunoassay reacts with neither sufentanil metabolites formed by oxidative metabolism nor with possible products of hydrolysis of sufentanil (2). Radioimmunoassay also confirmed that none of drugs administered simultaneously interfered with the assay of sufentanil. The free fraction of sufentanil was measured by equilibrium dialysis in serum collected from each patient preoperatively and 30 min after induction of anesthesia using purified tritium-labelled sufentanil. In the preoperative serum sample, cold sufentanil was added to achieve a concentration of 1 ng/ml. Concentrations of albumin and α1-acid glycoprotein were measured using preoperative samples.

Plots of sufentanil concentration versus time were used to calculate the pharmacokinetic variables using a compartment model independent approach. The area under the curve from zero to infinity (AUC) was calculated by summing the value to the time of last sample (trapezoidal rule) and the extrapolated value with the rate constant of elimination (β) from the slope of the post distribution natural log of plasma concentration versus time relation determined by linear regression. Plasma clearance was determined by dividing dose by AUC. The total apparent volume of distribution (Vdβ) was measured by dividing dose by $\beta \times$ AUC. Statistical differences between the data obtained in patients with cirrhosis and in control patients were analyzed by the two-tailed nonparametric Mann-Whitney U-test, and linear regression was used to examine the relation between sufentanil protein binding and plasma protein levels, with $P <$ 0.05 taken as the minimum level of statistical significance.

Results

Preoperative biochemical data are reported in Table 2. The plasma concentrations of albumin and of α1-glycoprotein did not differ in the two groups (Table 2). The duration of anesthesia was 2.1 ± 0.7 hr in the control patients and 1.7 ± 0.8 hr in the patients with cirrhosis. The mean plasma concentrations of sufentanil did not differ between controls and cirrhotics at any sampling time. The plasma concentrations of sufentanil 30 min after its administration averaged 0.9 ± 0.1 ng/ml in control and 1.0 ± 0.1 ng/ml in cirrhotic patients. After 8 hr the plasma concentration of sufentanil was below the detection limit in half of the patients and, therefore, the pharmacokinetic interpretation was restricted to the first 8 hr after sufentanil administration. None of the pharmacokinetic variables differed between the two groups (Table 3).

Table 3. Pharmacokinetic Variables

	T1/2β* (hr)	Vdβ† (Lkg)	Cl‡ (ml·min^{-1}·kg^{-1})
Controls			
1	2.7	1.9	7.9
2	3.7	3.3	10.2
3	4.1	4.1	11.6
4	5.5	3.4	7.1
5	3.7	4.2	13.4
6	2.7	2.6	11.2
7	2.9	3.5	14.0
8	3.2	3.8	13.5
9	3.0	3.3	12.4
Mean ± SD	3.5 ± 0.9	3.3 ± 0.7	11.3 ± 2.5
Cirrhotics			
1	4.2	3.3	6.7
2	3.7	2.5	5.1
3	4.6	6.7	16.1
4	4.6	5.0	12.6
5	3.1	3.8	13.9
6	3.7	3.4	10.6
7	3.4	3.8	12.9
8	4.3	3.0	8.0
9	4.1	2.6	7.3
10	4.1	3.3	9.4
11	4.2	7.5	20.6
12	5.1	3.0	6.9
Mean ± SD	4.1 ± 0.6	4.0 ± 1.6	11.0 ± 4.6

*Elimination half-life.
†Total apparent volume of distribution.
‡Plasma clearance.

Table 4. Free Fraction of Sufentanil Not Bound to Plasma Protein

	Sufentanil free fraction (%)	
	Before induction of anesthesia	30 Min after induction of anesthesia
Controls	8.8	9.4
	6.1	8.3
	10.1	9.2
	6.7	7.5
	9.8	11.7
	6.8	7.2
	8.0	10.6
	8.3	7.4
	10	9.1
Mean ± SD	8.3 ± 1.5	8.9 ± 1.5
Cirrhotics		
	12.2	11.9
	12.0	12.4
	8.9	6.5
	9.0	9.0
	9.6	11.3
	10.7	11.9
	7.8	9.1
	11.1	11.9
	10.9	14.9
	7.3	12.3
	8.2	9.9
	7.4	8.0
Mean ± SD	9.6 ± 1.8	10.8 ± 2.3

The elimination half-life was of 3.5 ± 0.9 hr in controls and 4.1 ± 0.6 hr in cirrhotics; the plasma clearance was 11.3 ± 2.5 ml·min^{-1}·kg^{-1} in controls and 10.8 ± 4.6 ml·min^{-1}·kg^{-1} in cirrhotics. The total apparent volume of distribution (Vdβ) did not differ between the two groups (3.3 ± 0.7 L/kg in controls and 4.0 ± 1.6 L/kg in cirrhotic patients).

The unbound fraction of sufentanil added to preoperative samples was 8.3 ± 1.5% in control patients (Table 4). In patients with cirrhosis the unbound fraction of sufentanil added to preoperative samples, 9.6 ± 1.8%, was not significantly different from the value observed in control patients. The unbound fraction measured 30 min after induction of anesthesia was similar to preoperative values and remained unchanged between the two groups.

Discussion

Sufentanil is, like most lipophilic drugs, almost completely metabolized by the liver before its excretion. In view of the elimination profile of sufentanil in normal patients, alteration of its pharmacokinetics, especially during the elimination phase, is expected in patients with cirrhosis. However, in the present study no alteration of sufentanil pharmacokinetics was observed in patients with cirrhosis. There are several possible explanations for this finding. In view of its pharmacokinetic profile, sufentanil, highly extracted by the liver, has a high plasma clearance. Therefore sufentanil plasma clearance should be influenced by the liver blood flow and not by the degree of plasma protein binding or the intrinsic activity of the liver monooxygenase system.

Thus, the present results suggest that hepatic blood flow was not reduced to a greater extent in cirrhotic patients than in control patients. Most of the cirrhotic patients had portal hypertension as evidenced by the number having had sclerosing injections of esophageal varices, which suggests that blood flow through the functional hepatocytes (3) was reduced. Abdominal surgery is associated with decreases in hepatic blood flow (4) and, therefore, with decreases in clearance of highly extracted drugs such as sufentanil. However, there was no difference in sufentanil clearance in control patients between those having abdominal surgery and those having orthopedic operations. Furthermore, plasma clearance in our control patients was similar to that observed in another study of patients undergoing nonabdominal surgery (5).

A second possible explanation for the observed absence of differences in sufentanil pharmacokinetics in normal and cirrhotic patients is related to the fact that, as a highly lipophilic compound, sufentanil has a large volume of distribution, similar to that of fentanyl. For such compounds, detection of differences in elimination kinetics may be hindered by the large volume of distribution. With fentanyl (6) as well as in the present study with sufentanil, we were unable to demonstrate pharmacokinetic alteration in patients with uncomplicated cirrhosis (6), whereas with alfentanil, which distributes in much smaller volume, plasma clearance is reduced in cirrhotic patients with the same degree of hepatic dysfunction as in the present study (7).

Finally, pharmacokinetic studies of sufentanil are limited by the detection limit of the method used for measurement of plasma concentrations of sufentanil. Even after a large bolus dose of sufentanil (3 μg/kg), the plasma concentration of sufentanil becomes undetectable after 8 or 10 hr in most patients.

Although plasma protein binding of alfentanil is altered in cirrhotic patients (8), in the present study no change in the plasma free fraction was observed with sufentanil in cirrhotics. The unbound fractions of sufentanil measured in serum samples obtained before and 30 min after sufentanil administration were similar. In all samples, the unbound fraction was determined at a total sufentanil concentration of approximately 1 ng/ml. Even if the concentration had been different among the samples, it would not have influenced the results because the unbound fraction of sufentanil remained unchanged over the concentration range of sufentanil of 0.1 to 10 ng/ml (9). Sufentanil, along with many basic drugs, is mainly bound to α1-glycoprotein, but there is no correlation between the α1-glycoprotein concentration and the degree of sufentanil plasma binding (9). In our patients with cirrhosis, neither the α1-glycoprotein nor the albumin plasma concentration differed from controls and this may partly explain why the sufentanil free fraction remained unaffected.

In conclusion, the lack of significant difference in sufentanil elimination kinetics and plasma protein binding in cirrhotic and non-cirrhotic patients that we studied suggests that sufentanil in a single dose does not exert a prolonged effect in patients with uncomplicated cirrhosis.

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Ketamine Potentiates Nondepolarizing Neuromuscular Relaxants in a Primate

Shen Kou Tsai, MD, and Chingmuh Lee, MD

TSAI SK. LEE C. Ketamine potentiates nondepolarizing relaxants in a primate. Anesth Analg 1989;68:5–8.

Ketamine has many neuromuscular effects in vitro. Its neuromuscular effects in vivo have been controversial and inconsistent. To systematically examine its neuromuscular effects over a wide dose range and its interaction with all popular nondepolarizing neuromuscular relaxants, the effects of ketamine 2, 5, and 10 mg/kg IV were studied on a continuous but incomplete (50%) neuromuscular block preestablished by an IV infusion of d-tubocurarine, atracurium, vecuronium, and pancuronium. Indirectly stimulated adductor pollicis muscle response of monkeys anesthetized with 0.5–1.0% halothane in oxygen were quantified. Ketamine in the absence of a neuromuscular relaxant had no effect on the thumb twitch. In a dose-dependent manner, ketamine significantly enhanced the 50% depression of the thumb twitch preestablished by a constant IV infusion of each of the four muscle relaxants studied. Ketamine 2 mg/kg potentiated the neuromuscular relaxants in the following order of magnitude: vecuronium > atracurium > d-tubocurarine > pancuronium. However, with a 10 mg/kg dose of ketamine, pancuronium became as potentiated as was vecuronium, i.e., pancuronium = vecuronium > atracurium > d-tubocurarine. It is concluded that in the primate, ketamine potentiates all nondepolarizing muscle relaxants in a dose-dependent manner.

Key Words: ANESTHETICS—intravenous. NEUROMUSCULAR RELAXANTS—ketamine potentiation. INTERACTIONS, DRUG—ketamine and relaxants.

Ketamine is used to induce and to maintain general anesthesia (1). Conflicting results have been reported on whether ketamine potentiates the neuromuscular effect of muscle relaxants. The in vitro study of Wilson (2) suggested that ketamine not only increased twitch height in the isolated rat phrenic nerve–diaphragm preparation, but also paradoxically enhanced the effect of nondepolarizing neuromuscular blocking agents. Amaki et al. (3) demonstrated that ketamine had an inhibitory effect on presynaptic acetylcholine synthesis or release. Maleque et al. (4) observed a predominant postjunctional effect of ketamine in blocking the acetylcholine-activated ionic channels in open conformation. In vivo, Bogdan et al. (5) reported that ketamine in rabbits enhanced the action of depolarizing neuromuscular relaxants and had no effect on nondepolarizing relaxants. In a clinical setting, Corssen et al. (6) and Domino et al. (1) found that the tone of the masseter and temporal muscles increased after ketamine induction of anesthesia. Radnay and Badola (7) reported that ketamine produced generalized extensor spasm in infants. In humans, Johnston et al. (8) studied a single dose of ketamine (75 mg/m^2 body surface area) and found that it enhanced the neuromuscular blocking effect of *d*-tubocurarine but not that of pancuronium.

There appears to be a need for a systematic study of a wide dose range of ketamine interacting with all commonly used nondepolarizing neuromuscular blocking relaxants. The present study of neuromuscular effects of ketamine reconciles the difference between *d*-tubocurarine and pancuronium and adds their congeners, atracurium and vecuronium.

Materials and Methods

The study was approved by the Institutional Review Board. Thirty-three adult male monkeys (Macaca cyclopis) weighing 5–7 kg were heavily sedated with

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Address correspondence to Dr. Lee, Professor and Chairman, Department of Anesthesiology, Harbor–UCLA Medical Center, 1000 W. Carson Street, Torrance, CA 90509.

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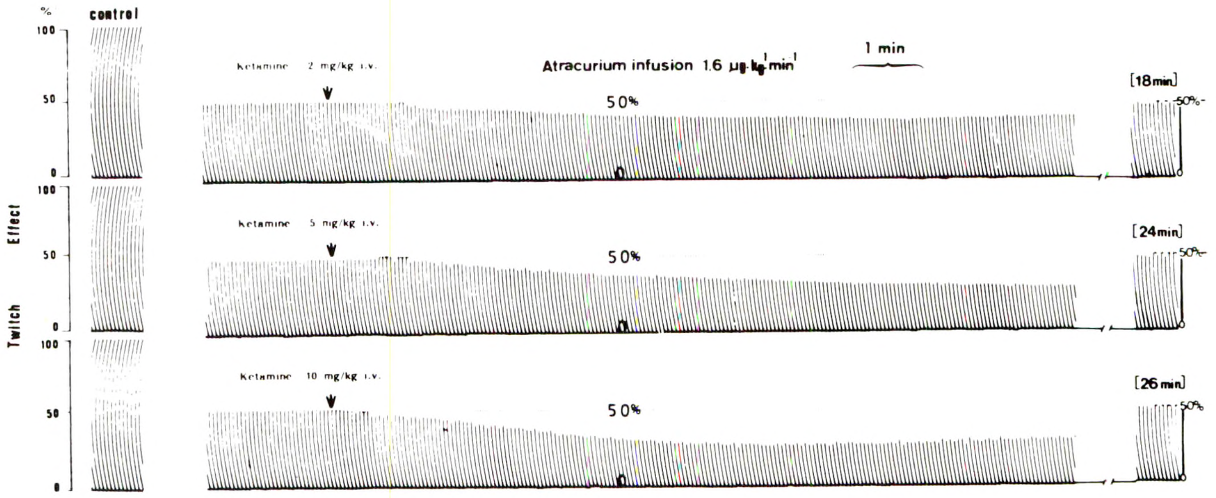

Figure 1. Recordings from typical experiments that show the effect of IV ketamine 2 mg/kg (top), 5 mg/kg (middle), and 10 mg/kg (bottom) on a constant 50% twitch depression produced by atracurium infusion.

methohexital 10–15 mg/kg IM. Two IV lines were inserted, one in each lower limb. Dextrose 5% in water was infused IV at 5 $ml \cdot kg^{-1} \cdot hr^{-1}$. Ketamine and muscle relaxants were given through separate IV lines. The trachea was intubated without the use of muscle relaxants and anesthesia was maintained with halothane 0.5–1% in oxygen. End-tidal CO_2 and halothane concentration were monitored with a Datex Normocap CO_2 monitor and a Datex anesthetic gas monitor. Ventilation was controlled by a Harvard Apparatus respiration pump to keep end-tidal CO_2 at 30–40 mm Hg. Esophageal temperature was maintained at 35–37°C with a heating lamp and a thermoblanket. A catheter was placed in the anterior tibial artery to record blood pressure and to obtain blood samples for measurement of gas tensions. Arterial blood pH was 7.30–7.40.

The ulnar nerve was stimulated at the wrist through two 27-gauge needle electrodes at 0.1 Hz with 0.2 ms supramaximal pulses from a Grass S-88 stimulator and a Grass SIU5 Stimulus Isolation Unit. The force of thumb adduction was measured by a Grass FT-03 force transducer. The ECG, blood pressure, and thumb twitch were recorded on a four-channel Grass Polygraph recorder. The study did not begin until baseline responses had been stable for at least 30 minutes.

The control group of five monkeys received incremental doses of 2, 5, and 10 mg/kg ketamine administered intravenously at hourly intervals. Study groups of seven monkeys each received IV infusion of either *d*-tubocurarine, atracurium, vecuronium, or pancuronium to establish and maintain a steady depression of the thumb twitch for 15 minutes at 50% of baseline. The same three incremental doses of ketamine (2, 5, and 10 mg/kg IV) were then added sequentially through the other IV line. Between ketamine injections, the thumb twitch was allowed to recover to pre-ketamine levels. After the last dose of ketamine, the infusion of the nondepolarizing neuromuscular blocking relaxant was terminated when the thumb twitch had recovered to pre-ketamine level. On full recovery of the thumb twitch, halothane anesthesia was terminated and the monkeys were given postanesthesia care until fully recovered.

Results are presented as the mean ± SEM. The results were tested for statistically significant differences with the Wilcoxon signed rank test for matched pairs, $P < 0.05$ being regarded as significant.

Results

Ketamine alone in all three doses had no significant effect on the thumb twitch. The neurally evoked twitch tension of the adductor pollicis was maintained at near 50% of baseline (48 ± 3%) by an IV infusion of *d*-tubocurarine 1.7 ± 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$, atracurium 1.5 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, vecuronium 0.4 ± 0.01 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and pancuronium 0.3 ± 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The addition of ketamine 2, 5, and 10 mg/kg produced a dose-dependent further depression of the twitch (Figs. 1 and 2). The differences in twitch response from respective pre-ketamine values were statistically significant except that the 2 mg/kg dose of ketamine did not significantly potentiate pancuronium. The maximal twitch depression occurred within 5–15 minutes

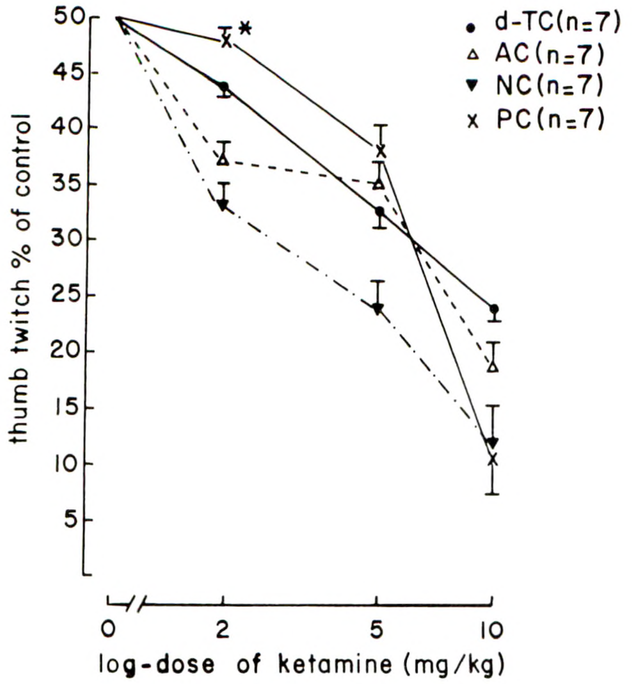

Figure 2. The dose-response curve of the acute effect of IV ketamine administration on a preexisting 50% twitch depression of thumb adduction produced by continuous infusion of four muscle relaxants (vertical bars indicate SEM). All values are significantly different from the pre-ketamine values, $P < 0.01$, except $^*P > 0.05$. dTc, *d*-tubocurarine; AC, atracurium; NC, vecuronium; PC, pancuronium.

Table 1. Duration of Ketamine Potentiation of Near-50% Neuromuscular Block Preestablished by IV Infusion of Nondepolarizing Neuromuscular Blocking Agents*

	Ketamine dose (mg/kg)		
	2	5	10
d-Tubocurarine (min)	22.0 ± 2.2	36.0 ± 1.4	50.0 ± 2.1
Atracurium (min)	16.8 ± 1.0	18.2 ± 1.2	32.2 ± 2.0
Vecuronium (min)	18.5 ± 1.5	28.6 ± 1.6	36.0 ± 2.0
Pancuronium (min)	—†	36.6 ± 2.2	61.0 ± 6.3

*Mean ± SEM; $n = 7$.
†No consistent effect of ketamine (see Fig. 2).

after ketamine administration (Fig. 1). The duration of potentiation was 32–61 min with the 10 mg/kg dose of ketamine (Table 1).

The maximal depression of the mean arterial blood pressure was 15 ± 2% (6–14 mm Hg) and the heart rate decreased by 12 ± 3% at the same time. All monkeys recovered completely after the experiments.

Discussion

In preliminary studies we determined that the ED_{50} values of the nondepolarizing neuromuscular blocking relaxants in the ulnar nerve-adductor pollicis muscle preparations of Macaca cyclopis monkeys during 0.5–1% halothane anesthesia were: *d*-tubocurarine 0.17 mg/kg; atracurium 0.1 mg/kg; vecuronium 0.01 mg/kg, and pancuronium 0.012 mg/kg. These values put the Macaca cyclopis very close to humans in terms of relative neuromuscular sensitivity. We therefore assume that our observation may have clinical relevance. Brittan and Tyers (9), as well as Hughes (10) made similar observations in another species of monkey. To maximize comparability of results, we did the entire study under the basal halothane anesthesia to correspond with the clinical study of Johnston et al. (8).

Our study demonstrated that under basal halothane anesthesia, bolus doses of ketamine up to 10 mg/kg had no neuromuscular blocking or stimulating effect in the primate in the absence of other neuromuscular relaxants. Because ketamine is rarely used in such high doses in clinical practice, it can be safely said that if ketamine causes apnea in the absence of other relaxants or increases muscle tone, it does so centrally. A neuromuscular blocking effect of ketamine in vivo is not demonstrable even if relatively large doses of ketamine are added to the neuromuscular effect of halothane. In the presence of nondepolarizing neuromuscular relaxants, however, ketamine consistently potentiated the neuromuscular block in a dose-dependent manner. That ketamine 2 mg/kg was insufficient to potentiate pancuronium indicates only that the slope of the dose-response curve of the interaction between ketamine and pancuronium is different from that between ketamine and the other relaxants studied. Although 2 mg/kg of ketamine potentiated *d*-tubocurarine but not pancuronium, larger doses of ketamine potentiated pancuronium more than *d*-tubocurarine (Fig. 2). By preestablishing a 50% neuromuscular block with steady infusion of the neuromuscular blocking relaxant, we put the neuromuscular preparation on the steepest portion of the dose-response curve, namely, at a point where any additional neuromuscular effect would be most readily demonstrated. By using each monkey as its own control, by using monkeys of uniform size, sex, and species, and by studying a wide dose range of ketamine, we eliminated many factors that might have obscured the neuromuscular effect of ketamine. Johnston et al. (8) studied only one dose of ketamine, 75 mg/m^2 body surface area. Individual variability and incomplete dose range of ketamine probably led them to conclude that ketamine did not potentiate pancuronium. We conclude instead that ketamine potentiates all nondepolarizing neuromuscular relaxants studied, but with different dose-response curves. To the best of our knowledge, potentiation of the neuromuscular effects of atracurium and vecuronium by ketamine has not been documented in the primate or clinically.

Johnston et al. (8) attempted to explain the neuromuscular effect of ketamine, especially its different potentiating effects on *d*-tubocurarine and on pancuronium on the basis of differences in protein binding of the relaxants. Since then, several new neuromuscular actions of ketamine have been proposed from in vitro studies. Each of these several actions may have its own threshold, potency, and plateau. The most recent studies suggest that ketamine acts on neuromuscular transmission mainly by interfering with acetylcholine-activated ionic channels on the postjunctional endplate (4,11). Ketamine appears to lack affinity for acetylcholine receptors (12,13), and only slightly reduces acetylcholine output (3,4). Regarding the ionic channel, Maleque et al. (4) concluded that ketamine blocked the acetylcholine-activated ionic channel in the open conformation. Wachtel (11) concluded instead that ketamine reduced the average lifetime of the acetylcholine-activated ionic channel but not necessarily by sequentially blocking it in open conformation. Typically, channel-blocking drugs do not block neuromuscular transmission enough by themselves to depress the neurally evoked thumb twitch in vivo. In the presence of other neuromuscular blocking relaxants, they may enhance neuromuscular block by their channel effect.

The mechanism of the interaction between ketamine and relaxants cannot be determined in our study. A given dose of ketamine may potentiate the muscle relaxants in different ways because the muscle relaxants differ in the relative importance of their prejunctional and postjunctional (receptor-occupying and channel-blocking) effects. Similarly, different doses of ketamine may have different profiles of potentiation of the muscle relaxants because ketamine has different dose-response curves for its various neuromuscular actions. Its prejunctional, protein-binding, receptor-occupying, and channel-blocking effects probably have different thresholds, slopes, and plateaus.

Recently, fade of tetanic and of train-of-four responses has been used as an indicator of the prejunctional effects of curariform muscle relaxants (10,14). However, fade is not expected to differentiate prejunctional from postjunctional channel-blocking effects. Furthermore, tetanic stimulation alters the twitch response and the infusion requirement of the relaxants and is therefore not advantageous in interaction studies.

In summary, ketamine, in a dose-dependent manner potentiates the neuromuscular blocking effect of *d*-tubocurarine, pancuronium, atracurium, and vecuronium in the primate. The literature describes numerous neuromuscular effects of ketamine in vitro but suggests that its effects on the acetylcholine-dependent ionic channels may be the main mechanism of its neuromuscular action in vitro. The changing profile of ketamine interactions with different nondepolarizing neuromuscular relaxants in vivo can be explained by the diversity of neuromuscular actions of both ketamine and the muscle relaxants.

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Electroencephalographic Burst Suppression in Elderly and Young Patients Anesthetized with Isoflurane

Arthur E. Schwartz, MD, Robert H. Tuttle, MD, and Paul J. Poppers, MD

SCHWARTZ AE, TUTTLE RH, POPPERS PJ. Electroencephalographic burst suppression in elderly and young patients anesthetized with isoflurane. Anesth Analg 1989;68:9–12.

The electroencephalograms of seven elderly (70–85 years) and seven younger patients (23–31 years) anesthetized with a concentration of isoflurane sufficient to produce burst suppression were studied. Anesthesia in these unpremedicated subjects was induced by inhalation of nitrous oxide, isoflurane, and oxygen. Tracheal intubation was facilitated with succinylcholine and the lungs were next ventilated with oxygen and isoflurane to produce an end-tidal concentration of 1.7%. Isoflurane concentration was determined by infrared analysis of expired gas collected from a Teflon catheter inserted through the endotracheal tube. After 25 minutes at steady state, the EEG was recorded for 5 minutes prior to surgical stimulation. Arterial blood pressure, temperature, and ventilation were maintained at normal values. In elderly patients the EEG had both a greater proportion of total time in electrical silence (76.0 ± 10.8% vs 37.6 ± 15.4%; $P < 0.01$) and a greater number of isoelectric periods (19.7 ± 8.1 vs 10.7 ± 5.4; $P < 0.05$). This demonstrates a discrete alteration with age in the central nervous system sensitivity to isoflurane.

Key Words: ANESTHESIA—geriatric. ANESTHETICS, VOLATILE—isoflurane. BRAIN—electroencephalogram. AGE—EEG responses.

Aging is associated with physiological changes that may alter drug action. Stevens et al. reported an age-related reduction in the minimum alveolar concentration (MAC) of isoflurane (1). In patients over 55 years of age, MAC was 1.05% compared with 1.28% in patients between the ages of 19 and 30 years. Similarly, Gregory et al. found a decrease in halothane MAC with aging (2).

Increasing concentrations of isoflurane are known to produce a progressive effect on the EEG from continuous activity at 1.2% to burst suppression at higher concentrations to complete electrical silence at 2.5% (3). Burst suppression is characterized by alternating periods of electrical silence disrupted by bursts of high voltage activity. The duration of electrical silence increases with increasing anesthetic dose. These EEG effects are associated in dogs with a dose-related decrease in cerebral oxygen consumption (4). This progresses until the onset of an isoelectric EEG, after which increasing anesthetic concentrations produced no further effect on cerebral oxygen consumption. These findings suggest that the cerebral metabolic changes produced by isoflurane are secondary to an effect on cortical electrical activity. The present study was designed to determine if an altered sensitivity to isoflurane in elderly humans is associated with changes in the threshold for EEG burst suppression.

Methods

This study was approved by the Institutional Committee on Research Involving Human Subjects. Informed written consent was obtained from seven elderly (70–85 years) and seven younger patients (23–31 years) scheduled for elective surgery. No patient had evidence of neurological, cardiac, or pulmonary disease and none was taking medication known to alter sensitivity to general anesthetics. Subjects received no premedication other than sodium citrate (30 ml) taken orally. General anesthesia was induced by inhalation of nitrous oxide (70%) and oxygen with progressively higher concentrations of isoflurane. Ni-

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Address correspondence to Dr. Schwartz, College of Physicians and Surgeons of Columbia University, 630 West 168 Street, New York, NY 10032-2784.

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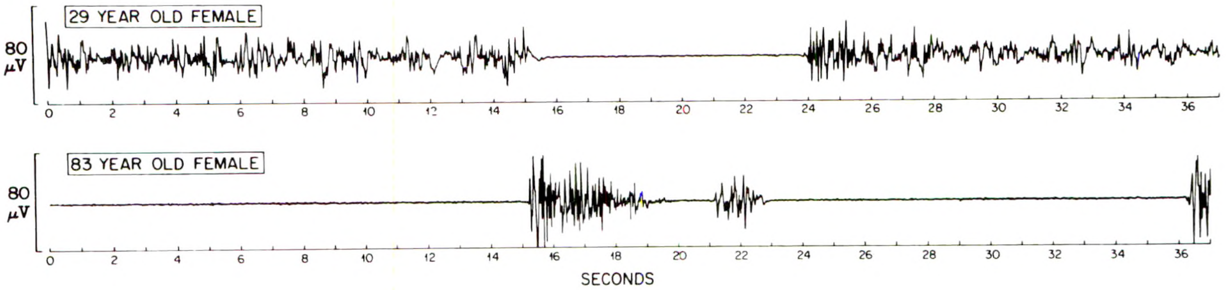

Figure 1. Typical electroencephalograms of an elderly and a younger patient given isoflurane to produce a steady state end-tidal concentration of 1.7%

trous oxide was discontinued before succinylcholine, 1 mg/kg, was injected IV to facilitate tracheal intubation. Recovery from neuromuscular blockade was documented by response to electrical stimulation of the ulnar nerve. Patients were mechanically ventilated with oxygen (5 L/min fresh gas flow) and isoflurane. The inspired concentration of isoflurane was adjusted to produce an end-tidal concentration of 1.7%, as measured by infrared analysis with a Puritan Bennett Anesthestic Agent Monitor 222 (Wilmington, MA). The device has a sensitivity of 0.1 vol% and a maximum rise time of 600 msec. For each patient, the analyzer was calibrated with a known concentration of anesthetic and at 0%. Exhaled gas was obtained from a 13-cm, 16-gauge Teflon catheter (Angiocath) inserted through the endotracheal tube. A 1-m length of narrow-bore nylon tubing with Luer locks connected the catheter hub to the analyzer. Ventilation was controlled at a rate of 8 breaths/min with a North American Drager anesthesia machine using a semi-closed circle circuit. End-tidal carbon dioxide tension was measured by infrared analysis (Siemens) and maintained between 35 and 42 mm Hg. All patients were horizontal and supine during the study. Esophageal temperature was maintained between 35.5 and 36.2°C with warming blankets. Arterial blood pressure was measured by an automated oscillometer (Omega 1400) and maintained within 15% of preinduction value by intravenous infusion of lactated Ringer's solution or phenylephrine. Phenylephrine was chosen because of its lack of effect on cerebral blood flow, cerebral metabolic rate, and EEG (4).

After 25 minutes of a continuous 1.7% end-tidal isoflurane concentration, the electroencephalogram was recorded for 5 minutes prior to surgical stimulation. Operating room noise was kept at a minimum to prevent auditory stimulation. Bifrontal leads (Fp1, Fp2) were used with a Neurotrac monitor (Interspec, Conshohocken, PA). The Neurotrac device uses a highpass filter of 30 Hz (−3db at 30 Hz, 60 db/decade) and a single pole lowpass filter of 4 Hz (−3 db at 4 Hz, 20 db/decade). The filter design was employed to minimize the electrical interference associated with the operating room environment. Electrode placement was adjusted until impedences were all below 5000 ohms. The EEG signal was stored on magnetic tape by a Vetters 8 track recorder (Rebersburg, PA) and analyzed from the output of a Hewlett Packard 78172A annotating recorder (Andover, MA). Electroencephalogram recordings were analyzed for duration of electrical silence, which was expressed as a percentage of the total 5-minute study period. The criteria for isoelectricity were met if there were no wave forms, no rhythmicity and voltage was less than 5 µV. The frequency of isoelectric events was determined by counting the number of times an uninterrupted, electrically silent interval was observed during the 5-minute study period. A comparison of the duration and frequency of isoelectricity, end-tidal carbon dioxide tension, mean blood pressure, and temperature between elderly and younger patients was made by Student's *t*-test for unpaired data (two-tailed). $P < 0.05$ was considered statistically significant.

Results

All patients showed EEG burst suppression at 1.7% end-tidal isoflurane concentration. Typical electroencephalograms of an elderly and younger patient are seen in Figure 1. However, as seen in Table 1, in the elderly patients the proportion of time in electrical silence was significantly greater than that observed in younger controls (76.0 ± 10.8% vs 37.6 ± 15.4%, mean ± SD). In addition, the frequency of isoelectric EEG events was significantly greater in the elderly subjects (19.7 ± 8.1 vs 10.7 ± 5.4). Phenylephrine was administered to four elderly (100–300 µg) and two young (200 µg) patients. There were no differ-

Table 1. Burst Suppression at 1.7% End-Tidal Isoflurane Concentration

	Elderly	Young	*P*
n	7	7	—
Sex (M/F)	3/4	2/5	—
Age (yr)*	78.1 ± 5.0	28.3 ± 2.6	—
Isoelectric time (percent)*†	76.0 ± 10.8	37.6 ± 15.4	<0.01
Number of isoelectric intervals*†	19.7 ± 8.1	10.7 ± 5.4	<0.05

*Values are mean ± SD.
†During 5-minute period of measurement.

Table 2. Physiological Data

	Elderly	Young	*P*
MAP (mm Hg)	87.3 ± 7.2	80.0 ± 12.5	<0.3
$ETCO_2$ (mm Hg)	39.0 ± 2.4	38.1 ± 2.9	<0.6
Temperature (°C)	35.7 ± 0.3	35.8 ± 0.5	<0.9

Values are mean ± SD.
Abbreviations: MAP, mean arterial pressure; $ETCO_2$, end-tidal carbon dioxide tension.

ences in blood pressure, end-tidal CO_2, or temperature between elderly and young subjects (Table 2).

Discussion

Altered sensitivity to anesthetics in elderly patients has been widely reported (5,6). These changes in drug action are due to age-related alterations in drug disposition, end-organ sensitivity, or a combination of both. The dose of thiopental required to achieve EEG burst suppression in adults decreases linearly with age (7). This is explained by an age-related change in the initial volume of distribution of the drug. For muscle relaxants as well, the more profound response seen in elderly subjects can be explained by a difference in pharmacokinetics, with no evidence of an alteration in sensitivity at the neuromuscular junction (8). For narcotics, both pharmacokinetic and pharmacodynamic changes may play a role in age-related differences in effect. Bentley et al. reported a prolongation in the elimination half-life of fentanyl with age (9). In contrast, Scott and Stanski showed no age-related changes in the pharmacokinetics of fentanyl or alfentanil, but demonstrated a 50% reduction in dose requirements with increasing age (from 20 to 89 years) using EEG power spectral analysis (10). Sufentanil has both a decreased plasma clearance and a prolonged respiratory depressant effect in elderly patients (11). For isoflurane, however, the more profound effect in older patients when compared to younger controls is due to an increased central nervous system sensitivity to the same concentration of isoflurane. The use of EEG burst suppression in this study allowed quantification of anesthetic effect at a clinically relevant depth of anesthesia (12).

The encephalogram was studied in order to quantitate the effect of isoflurane on the brain. The evoked potential, in contrast, reflects the function of the sensory receptor and all pathways between that receptor and the neural generators monitored. Age-related alterations in the effects of isoflurane on evoked responses would be expected. However, these changes could not be confidently attributed to changes in the brain.

Alterations in drug action in the elderly may be due to morphological, physiological and/or biochemical changes. There is, for example, a decrease in neuronal density with age resulting in a 30% reduction in neurons, particularly in the cerebral cortex, between 20 and 90 years (13,14). Naber and Dahnke demonstrated a 5–15% reduction in brain protein content in the elderly (15). This is consistent with a decrease in cytoplasmic protein synthesis (16). In addition, neuronal functions mediated by catecholamines, acetylcholine, and gamma aminobutyric acid are reduced with age (17). There is also evidence of a decrease in cerebral oxygen consumption in old age. This is associated with a decrease in cerebral blood flow and an increase in cerebral vascular resistance (18).

The observation that the MAC of isoflurane decreases with age might be explained by changes in structure or function at any of the sites participating in a motor response to surgical incision. Hess et al. determined that sensitivity to noxious stimuli decreases with increasing age (19). Electromyogram study in the elderly suggests a decrease in the number of axons supplying peripheral muscles and a decrease in the number of muscles supplied by each axon (20). This study demonstrates a discrete alteration in the electroencephalographic sensitivity to isoflurane in the elderly. The work of Newberg et al. linking the EEG effects of isoflurane to altered cerebral metabolism (4) suggests that this alteration reflects an increased cortical sensitivity with age.

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Dose–Response Relationships for Edrophonium and Neostigmine as Antagonists of Moderate and Profound Atracurium Blockade

François Donati, PhD, MD, FRCPC, Charles E. Smith, BSc, MD, FRCPC,
and David R. Bevan, MB, MRCP, FFARCS

DONATI F, SMITH CE, BEVAN DR. Dose–response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. Anesth Analg 1989;68:13–19.

To measure the ability of neostigmine and edrophonium to reverse moderate and profound atracurium blockade, dose–response relationships were established for these reversal agents given at 1% and 10% twitch height recovery. Eighty-five ASA I and II adult patients received atracurium, 0.4 mg/kg, during a thiopental–nitrous oxide–enflurane anesthetic. Train-of-four stimulation was applied every 12 seconds, and the force of contraction of the adductor pollicis muscle was recorded. Edrophonium, 0.1, 0.2, 0.4, or 1 mg/kg; neostigmine, 0.005, 0.01, 0.02 or 0.05 mg/kg; or no reversal agent was given when there was either 1% or 10% recovery of the first twitch response. With profound blockade, the slope of the edrophonium dose–response relationship was significantly flatter ($P < 0.05$) than that of neostigmine. The dose of neostigmine required to achieve 80% first twitch recovery (ED_{80}) after 10 minutes was 0.013 ± 0.003 mg/kg (mean ± SEM) if given at 10% recovery, and 0.032 ± 0.004 mg/kg if given at 1% recovery. The ED_{80} for edrophonium was 0.22 ± 0.04 mg/kg and 1.14 ± 0.33 mg/kg, respectively. These values corresponded to neostigmine:edrophonium potency ratios of 16.6 ± 3.5 and 35.3 ± 8.9 at 90% and 99% blockade respectively ($P < 0.006$). We conclude that the relative potency of neostigmine is greater than that of edrophonium for antagonism of profound atracurium blockade.

Key Words: ANTAGONISTS, NEUROMUSCULAR RELAXANTS—edrophonium, neostigmine. MONITORING—neuromuscular transmission, train-of-four. NEUROMUSCULAR RELAXANTS—atracurium, vecuronium.

Edrophonium has a more rapid onset of action than neostigmine when used to reverse nondepolarizing neuromuscular blockade (1,2). Its potency is approximately 1/12th to 1/16th that of neostigmine, when used to antagonize 90% blockade (2–4).

However, results in several studies suggest that edrophonium is less effective than neostigmine in the antagonism of profound neuromuscular blockade (5–7). These results were obtained assuming that neostigmine was 12 (5,6) to 14 (7) times as potent as edrophonium. No dose–response relationships were obtained with profound blockade. Therefore, although it appears that edrophonium may be less effective than neostigmine against profound blockade, a larger dose of edrophonium may be as efficacious as neostigmine (5). Furthermore, because dose–response relationships have not been determined in the presence of profound blockade, the neostigmine: edrophonium potency ratio has not been established under these conditions.

This study was designed to determine dose–response relationships of edrophonium and neostigmine when administered to antagonize moderate (90%) and profound (99%) blockade, in order to establish potency ratios between the two reversal agents.

Patients and Methods

The protocol was approved by the Hospital Ethics Committee and informed consent was obtained from the patients. Eighty-five ASA physical status I or II were studied during various surgical elective procedures. Patients with hepatic, renal, or neuromuscular

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Address correspondence to Dr. Donati, Department of Anaesthesia Royal Victoria Hospital 687 Pine Ave. W., Montreal, Quebec, Canada H3A 1A1.

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disease were excluded, as were those with abnormal serum electrolyte levels and those taking any medication that might interfere with neuromuscular function.

Premedication with atropine, 0.006–0.01 mg/kg, or glycopyrrolate, 0.003–0.005 mg/kg, and morphine, 0.1 mg/kg, or meperidine, 1 mg/kg, was given intramuscularly 1 hour before the scheduled start of the surgical procedure. On arrival in the operating room, ECG was monitored continuously, and arterial blood pressure was measured noninvasively by oscillotonometry (DINAMAP). Anesthesia was induced with thiopental, 3–5 mg/kg, and maintained with nitrous oxide, 70%, and enflurane, 0.5–1.5% inspired, in oxygen. The ulnar nerve was stimulated supramaximally at the elbow with square pulses of 0.2 msec duration, delivered at a frequency of 2 Hz for 2 seconds (train-of-four), and repeated every 12 seconds. The hand and forearm were immobilized in a splint, and the force of contraction of the adductor pollicis muscle was measured with a force-displacement transducer (Grass FT-10) and recorded on paper. After a stable neuromuscular response was established, atracurium, 0.4 mg/kg, was given. Tracheal intubation was performed when neuromuscular response was abolished. Mechanical ventilation was then instituted by means of a Mapleson D circuit with a fresh gas flow of 70 ml·kg^{-1}·min^{-1}. After tracheal intubation, the inspired enflurane concentration was maintained at a constant level throughout the study, and anesthesia was supplemented, if required, with incremental doses of fentanyl.

When first twitch height had recovered to either 10% or 1% of its initial value, the patients received neostigmine, 0.005, 0.01, 0.02, or 0.05 mg/kg, or edrophonium, 0.1, 0.2, 0.4, or 1 mg/kg, or no reversal agent. The selection was made by random allocation. Each dose of each reversal agent was given to ten patients, five at each of the two levels of blockade studied. Five patients did not receive any reversal agent. Atropine, 0.3–1.8 mg, was administered when appropriate. No additional reversal agent was given for the next 10 minutes to patients to whom the reversal agent was given when first twitch recovery was 10%, and for the next 15 minutes in patients given the reversal agent at 1% recovery. At the end of the surgical procedure, an additional dose of reversal agent was given if required.

The height of the first twitch (T1) was measured once a minute after administration of the reversal agent and expressed as a percentage of initial control. The train-of-four ratio (T4/T1) was also calculated. The logit transformation (8) was applied to T1 and T4/T1. Dose-response relationships were determined for each reversal agent, at each minute after their administration, and for each level of blockade. These were calculated by linear regression of the logit transformation of the neuromuscular response (either T1 or T4/T1) against the logarithm of the dose. From these, the doses expected to produce 50% and 80% recovery of T1 (ED_{50} and ED_{80}) were interpolated, with the standard error of estimate for the mean (9). The effect of profound blockade was assessed by comparing the ED_{50} and ED_{80} obtained with each drug at 1% and 10% blockade. The neostigmine:edrophonium potency ratio, defined as the ratio of edrophonium to neostigmine ED_{50} or ED_{80}, was calculated for each level of blockade. Similar calculations were made for the T4/T1 response, and in this case, the ED_{50} and ED_{70} were evaluated and compared. These levels of recovery were chosen to allow comparisons to be made with previous studies (2–4). Comparisons were made using the Student's *t*-test applied to the logarithmic transformation of the values, and results were considered statistically significant when the *P* value was less than 0.05.

Table 1. Demographic Data

Group*	Age (yrs)†	Sex (M/F)	Weight (kg)†
Edrophonium 1%	51.6 ± 4.3	13/7	70.2 ± 2.5
Neostigmine 1%	52.2 ± 4.9	7/13	66.0 ± 2.6
All 1%	51.9 ± 2.9	21/19	68.1 ± 1.8
Edrophonium 10%	52.3 ± 2.2	6/14	65.8 ± 2.7
Neostigmine 10%	47.8 ± 3.7	7/13	63.1 ± 2.9
All 10%	50.1 ± 2.2	13/27	64.5 ± 1.8
No reversal	53.8 ± 6.2	3/2	71.2 ± 3.4

*1% and 10% refer to first twitch height when reversal agent was given.
†Values are mean ± SEM.

Results

The patients' demographic characteristics are shown in Table 1. There were no statistically significant differences between the study groups with respect to sex, age, or weight. Time from injection of atracurium to 1% and 10% twitch height recoveries were 31.0 ± 1.0 and 37.9 ± 1.3 minutes (mean ± SEM), respectively. There were no statistically significant differences between the groups before the administration of the reversal agent (Table 2).

Both first twitch height and train-of-four ratio recovery were greater with any dose of neostigmine or edrophonium than without any reversal drug. The degree of recovery increased with time after administration of the reversal drug and with the dose given

Table 2. Duration of Action of Atracurium

Group*	Time from injection to 1%	Time from injection to 10%	Time from 1 to 10%
Edrophonium 1%	31.5 ± 2.0	—	—
Neostigmine 1%	34.3 ± 1.5	—	—
All 1%	32.9 ± 1.2	—	—
Edrophonium 10%	30.4 ± 2.2	38.2 ± 2.0	7.8 ± 0.6
Neostigmine 10%	28.4 ± 2.1	37.2 ± 2.1	8.6 ± 0.6
All 10%	29.4 ± 1.4	37.7 ± 1.3	8.2 ± 0.4
No reversal	31.8 ± 3.4	39.0 ± 2.1	7.2 ± 0.7

Values are mean ± SEM.
*1% and 10% refer to first twitch height when reversal agent was given.

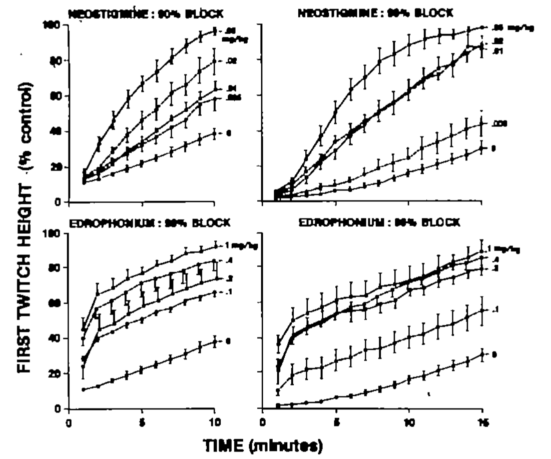

Figure 1. First twitch height against time after administration of the reversal agent (top: neostigmine; bottom: edrophonium) at doses shown. Zero indicates recovery when no reversal agent was given. Pharmacological reversal was attempted at 10% first twitch height recovery (left) or 1% first twitch height recovery (right). Bars indicate standard error of the mean.

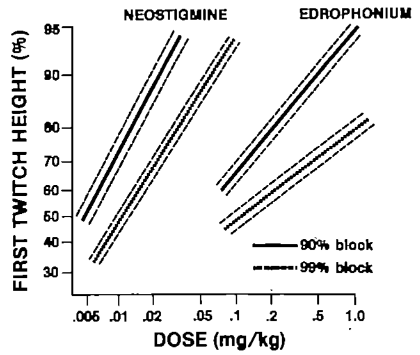

Figure 2. First twitch height (logit scale) vs dose (log scale) 10 minutes after administration of neostigmine and edrophonium given at either 1% (99% block) or 10% (90% block) first twitch recovery. Thin dashed lines represent the standard error of estimate for the mean.

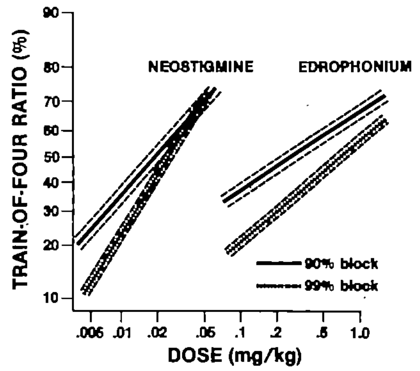

Figure 3. Train-of-four ratio (logit scale) vs dose (log scale) 10 minutes after administration of neostigmine and edrophonium given at either 1% (99% block) or 10% (90% block) first twitch recovery. Thin dashed lines represent the standard error of estimate for the mean.

(Fig. 1). At all doses, recovery was less if the reversal agent was given at 1% instead of 10% first twitch recovery. Edrophonium had a more rapid onset of action than neostigmine.

Dose–response relationships were determined based on data recorded 5, 7, 10, 12, and 15 minutes after the administration of the reversal agent. Figures 2 and 3 show these relationships at 10 minutes, for first twitch height and train-of-four ratio, respectively. When the reversal agent was given at 1% spontaneous recovery, the dose–response curve of both edrophonium and neostigmine was shifted to the right of the dose–response relationship determined when there was 10% spontaneous recovery, indicating loss of potency when used against profound blockade. However, the shift to the right was more pronounced for edrophonium (4–8 times) than neostigmine (1.5–3 times). For example, the first twitch height ED_{80}, 10 minutes after administration of neostigmine, was 0.013 ± 0.003 mg/kg with the reversal drug given at 10% recovery, compared with 0.032 ± 0.004 mg/kg, or 2.5 times as much, if given at 1% recovery ($P < 0.0015$). Corresponding values for edrophonium were 0.217 ± 0.045 mg/kg at 10% and 1.14 ± 0.33 mg/kg, or 5.3 times as much, at 1% ($P < 0.0001$). Thus, the neostigmine:edrophonium potency ratio was 16.6 ± 3.5 at 10% and 35 ± 9 at 1% ($P < 0.02$).

The dose–response curves for edrophonium were flatter than those for neostigmine, and statistical significance ($P < 0.05$) was achieved for both single twitch and train-of-four responses during profound (99%) blockade (Figs. 2, 3). Thus, the potency ratio varied depending on the level of blockade at which the comparison was made, being greater at more complete levels of recovery. Table 3 shows the calculated ED_{50}, ED_{80}, and potency ratios for first twitch height at various times after the reversal agent was given. Table 4 shows the calculated ED_{50} and ED_{70} for

Table 3. Potency in Relation to First Twitch Height*

	At 90% block	At 99% block	P
	Potency at 5 minutes		
ED$_{50}$			
Neostigmine	0.017 ± 0.004	0.042 ± 0.006	<0.002
Edrophonium	0.095 ± 0.023	0.330 ± 0.088	<0.001
Ratio	5.6 ± 1.1	7.9 ± 1.9	NS
	Potency at 7 minutes		
ED$_{50}$			
Neostigmine	0.008 ± 0.002	0.021 ± 0.003	<0.002
Edrophonium	0.067 ± 0.018	0.220 ± 0.075	<0.005
Ratio	8.4 ± 2.1	10.5 ± 2.7	NS
ED$_{80}$			
Neostigmine	0.034 ± 0.009	0.073 ± 0.011	<0.01
Edrophonium	0.43 ± 0.12	3.3 ± 1.1	<0.00005
Ratio	12.4 ± 3.0	45.6 ± 13.4	<0.002
	Potency at 10 minutes		
ED$_{50}$			
Neostigmine	0.005 ± 0.001	0.011 ± 0.001	<0.00002
Edrophonium	0.050 ± 0.010	0.11 ± 0.03	<0.02
Ratio	10.0 ± 2.1	10.0 ± 2.5	NS
ED$_{80}$			
Neostigmine	0.013 ± 0.003	0.032 ± 0.004	<0.0015
Edrophonium	0.22 ± 0.04	1.14 ± 0.33	<0.0001
Ratio	16.6 ± 3.5	35.3 ± 8.9	<0.006

*Values in mg/kg.

Table 4. Potency in Relation to Train-of-Four Ratio*

	At 90% block	At 99% block	P
	Potency at 7 minutes		
ED$_{50}$			
Neostigmine	0.035 ± 0.005	0.048 ± 0.004	<0.05
Edrophonium	0.40 ± 0.09	1.32 ± 0.24	<0.00005
Ratio	11.4 ± 3.0	27.5 ± 3.6	<0.0005
	Potency at 10 minutes		
ED$_{50}$			
Neostigmine	0.020 ± 0.003	0.026 ± 0.003	NS
Edrophonium	0.27 ± 0.07	0.81 ± 0.12	<0.001
Ratio	13.5 ± 1.8	31.2 ± 6.9	<0.002
ED$_{70}$			
Neostigmine	0.050 ± 0.007	0.049 ± 0.006	NS
Edrophonium	1.33 ± 0.36	2.95 ± 0.44	<0.001
Ratio	26.6 ± 3.7	60.0 ± 13.0	<0.002

*Values in mg/kg.

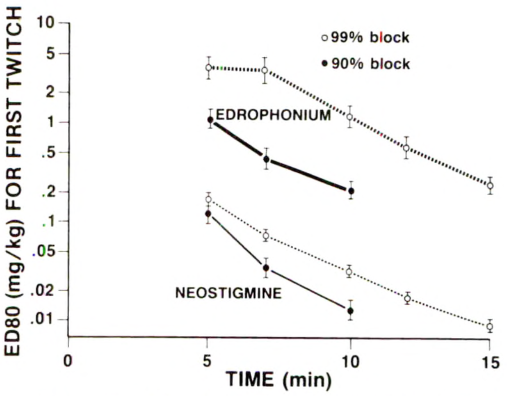

Figure 4. Calculated ED$_{80}$ for first twitch height for neostigmine and edrophonium, on log scale, vs time after their administration, when given at 1% (open circles) or 10% (closed circles) first twitch recovery. Error bars represent standard error of estimate for the mean. The potency difference between moderate and deep blockade is greater with edrophonium.

train-of-four ratio. The values which were omitted from these tables fell outside the range of doses tested.

The ED$_{80}$ for first twitch height and ED$_{50}$ for train-of-four ratio were plotted against time after injection of the reversal drug (Figs. 4, 5). The graphs demonstrate that the potency increases with time after the administration of the reversal drug. For example, 80% first twitch recovery is expected to be achieved with edrophonium, 0.5 mg/kg, in 6.5 minutes if given at 10% recovery, but only after 12.5 minutes if given at 1% recovery. With neostigmine, 0.04 mg/kg, the same result is expected in 6.5 and 9 minutes, respectively (Fig. 4). A train-of-four ratio of 50% will likely be obtained within 5.5 minutes after edrophonium, 0.5 mg/kg, if given at 10% recovery, but only after 13.5 minutes if injected at 1% recovery. With neostigmine, 0.04 mg/kg, the same train-of-four ratio will be reached in 6.5 and 8 minutes, respec-

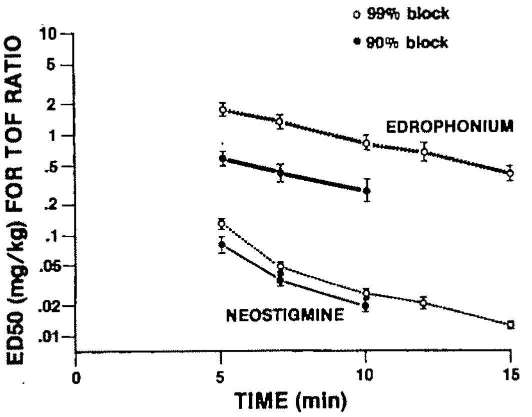

Figure 5. Calculated ED_{50} for train-of-four ratio, for neostigmine and edrophonium, on log scale, vs time after their administration, when given at 1% (closed circles) and 10% (open circles) first twitch recovery. Error bars represent the standard error of estimate for the mean. The potency difference between moderate and deep blockade is greater with edrophonium.

tively. The dose of neostigmine corresponding to a train-of-four ratio of 70% within 10 minutes was approximately 0.05 mg/kg, and the effect of such a dose was not markedly affected by the degree of blockade at the time of administration. However, edrophonium, 1 mg/kg, produced a train-of-four ratio less than 70% after 10 minutes if given at 10% recovery, and after 15 minutes if given at 1% recovery.

Discussion

This study shows that edrophonium, 0.1–1 mg/kg, and neostigmine, 0.005–0.05 mg/kg, both produce dose-dependent reversal of atracurium-induced neuromuscular blockade. The degree of reversal was inversely related to the intensity of neuromuscular blockade. However, these reversal agents were different in at least two respects: 1) the slope of the edrophonium dose–response relationship was flatter; and 2) the discrepancy between the potencies of neostigmine and edrophonium was greater when these drugs were administered to antagonize profound blockade.

Moderate blockade was defined as 10% recovery of first twitch height, which was the level chosen by a large number of investigators who studied the effects of reversal agents (1–4,7,10). Thus, comparisons can be made with other studies, especially those using pancuronium and *d*-tubocurarine with the same methodology (4). Recovery of first twitch height measured 10 minutes after the administration of edrophonium or neostigmine was greater if paralysis was produced with atracurium, as in this study, compared with longer-acting pancuronium or *d*-tubocurarine (4). At 10 minutes, the first twitch ED_{80} of neostigmine was 0.045 mg/kg after either pancuronium or *d*-tubocurarine (4), compared with only 0.013 mg/kg after atracurium. With edrophonium, the ED_{80} was 0.68 mg/kg and 0.88 mg/kg after pancuronium and *d*-tubocurarine, respectively (4), compared with 0.22 mg/kg after atracurium. Furthermore, examination of the curves of first twitch height as a function of time suggests that most of this improved recovery associated with atracurium administration occurred between 5 and 10 minutes after administration of the reversal agents. This pattern is most apparent with edrophonium, which attained a stable level of recovery after 2–3 minutes if the relaxant used was pancuronium or *d*-tubocurarine. With atracurium, edrophonium was associated with continued recovery up to at least 10 minutes. This finding suggests that the rapid decrease in the concentration of atracurium at the neuromuscular junction leads to improved recovery compared with pancuronium or *d*-tubocurarine, which are eliminated much more slowly.

Enflurane, the inhalation anesthetic used in the present study, potentiates atracurium neuromuscular blockade, and delays the time to 10% first twitch recovery (11). This implies that the reversal drug was given a longer time after injection of atracurium than if another anesthetic agent had been used, but it does not mean that pharmacologically assisted recovery was impaired once 1% or 10% recovery was attained. However, it appears that enflurane, 1.3–1.5% end-tidal concentration, slightly impairs neostigmine- (12) or edrophonium-assisted (13) recovery. The mean inspired concentration used in this study, 1%, corresponding to an end-tidal value of approximately 0.7%, was less than that used in the previous studies, and the effect of enflurane would be expected to be less. Nevertheless, the conditions used in this study may be considered as a "worst case situation", and assisted recovery could be at least as good if either another inhalation agent had been used or if enflurane had been discontinued.

At a given degree of atracurium blockade, we found the neostigmine:edrophonium potency ratio to depend on the time after administration of the reversal drug and the level of blockade at which comparisons were made. Edrophonium has a more rapid onset of action than neostigmine. Consequently, the potency ratio was relatively small shortly after reversal, but the discrepancy between the potencies of neostigmine and edrophonium increased with time. For 80% reversal of first twitch, the ratio was 12.4 at 7 minutes and 16.6 at 10 minutes. This compares with values of 12 to 19.5 found when antagonism of *d*-tubocurarine (2,4) or pancuronium (3,4) was attempted. When train-of-four ratios were compared, the dose of edrophonium required to produce 50% recovery was 11.4 times as large as that of neostigmine at 7 minutes and 13.5 times as large at 10 minutes. These values are less than the potency ratios obtained with pancuronium (24.8) and *d*-tubocurarine (28.6) (4).

However, the potency ratio was considerably greater at all levels of blockade for both first twitch and train-of-four ratio if the reversal agent was given at 99% blockade. For example, to produce 80% first twitch height within 10 minutes of the administration of the reversal agent, 0.013 mg/kg neostigmine or 0.22 mg/kg edrophonium (or 16.6 times as much) was required, if the reversal agent was given at 90% blockade. To achieve the same effect by giving the same drugs at 99% blockade, the dose of neostigmine needs to be increased by 2.5 times, to 0.032 mg/kg, but the dose of edrophonium needs to be increased 5.3-fold, to 1.14 mg/kg. Thus, the neostigmine:edrophonium ratio becomes 35.3. Because the edrophonium dose–response curve was flatter than that of neostigmine, this potency ratio is even greater at higher levels of recovery.

These results confirm many studies indicating that the effect of the reversal agent varies inversely with the intensity of the neuromuscular blockade at the time of its administration (5–7,14). Some studies have also suggested that neostigmine was preferable to reverse profound blockade, but the dose range was limited. Rupp et al. (5) found that edrophonium, 0.5 mg/kg, was associated with a longer time to 90% recovery than neostigmine, 0.04 mg/kg, if given when first twitch height was less than 10%. However, no difference was observed between edrophonium, 1 mg/kg, and neostigmine, 0.04 mg/kg (5). Thus, one could not determine whether the relative ineffectiveness of edrophonium, 0.5 mg/kg, was a consequence of the properties of the drug or of an appropriate choice of the potency ratio, which was assumed equal to 12. The problem was addressed in another article, where dose–response relationships were obtained for edrophonium and neostigmine as antagonists of 90% pancuronium blockade. For these relationships, equipotent doses were determined and given at 99% blockade. The results demonstrated that, based on potency ratios obtained at 90% blockade, edrophonium was less effective than neostigmine in the presence of profound blockade (7). The results of the present study suggest that this occurs because the slopes of the dose–response relationships of neostigmine and edrophonium are not parallel. Intensifying neuromuscular blockade could be seen as shifting the dose–response relationship down by a certain amount. This shift would have more effect on a flatter curve, i.e., that of edrophonium. Although one might speculate from these data that the two reversal drugs have different mechanisms of action, the cellular or molecular interactions which account for these differences are unclear and cannot be elucidated by our study.

Clinically, it appears preferable to avoid profound neuromuscular blockade. Time from 1% to 10% recovery is relatively short with atracurium (7–8 minutes), and waiting allows the use of smaller doses of edrophonium or neostigmine to obtain complete recovery in a few minutes. However, if one wishes to antagonize profound atracurium blockade, corresponding to one faint adductor pollicis twitch, neostigmine, 0.04–0.05 mg/kg, will probably produce adequate results, defined as a train-of-four ratio of 70% or greater (15), within 10–15 minutes. The doses of neostigmine required are smaller than those recommended to antagonize profound pancuronium blockade (7) most likely because of the rapid spontaneous recovery of atracurium. It is possible that edrophonium doses in excess of 1 mg/kg might be effective against profound blockade, but this study did not address this problem. Therefore, edrophonium should be avoided in the presence of profound blockade, at least until the safety and efficacy of very large doses (>1 mg/kg) are evaluated.

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Sixty-Seven Years Ago In
Anesthesia & Analgesia

P Cassidy: Experimental and clinical observations on Cotton process ether. Current Researches in Anesthesia and Analgesia: 1922;1:10–12.

This article is noteworthy for two reasons. First, it appears in volume 1, number 1 of the journal; the first issue of the first journal devoted exclusively to anesthesia. The publisher, the National Anesthesia Research Society, did not become the present International Anesthesia Research Society, still publishers of the journal, until 1925. F. H. McMechan, a founder of organized anesthesia in North America, was editor of the journal and executive secretary of the NARS.

The second reason this article is noteworthy is that it reflects both the eternal and still continuing quest for the ideal anesthetic, as well as the igenuity, sometimes misbegotten, of anesthetists involved in attempts to develop the ideal anesthetic agent (or piece of equipment). Cotton process either (CPE) is based on the same principle (or pious hope) as modern polypharmacy seen in much of anesthesia today: If one uses several drugs in anesthesia, the results will be better than if only one drug is used because the favorable effects of each of the drugs will summate or potentiate each other, thus offsetting the disadvantage of each other (and certainly never vice versa). CPE, named after its originator, one J. H. Cotton, consisted of a mixture of diethyl ("pure sulphuric") ether, carbon dioxide and ethylene compressed enough so that it existed in liquid form in a tin can. The theory was that ethylene (an explosive N_2O, if you will) speeds induction of anesthesia and decreases the amount of ether needed to maintain anesthesa while the CO_2 assures that the patient keeps breathing. CPE had been introduced well before 1922 but, as Cassidy points out, the problem was that the mixture was understandably so volatile that most of the contents of a can of this concoction were lost as soon as the can was opened. How, then, could it be used to produce inhalation anesthesia? Cassidy solved this problem by designing an architecturally absolutely bizarre but infinitely ingenious closed copper container in which he could open a can of CPE without losing its contents. The copper container then served as a vaporizer for gases delivered to the patient. Why copper? Because given the high specific heat and conductivity of copper, Cassidy reasoned that the container would, when put in a basin of hot water, maintain constant the concentrations of gases delivered. There would be no decrease in temperature of the container and so no decrease in concentration of ether delivered as a result of cooling due to heat loss associated with vaporization. Three decades later, Copper Kettles® were introduced as constant temperature ether vaporizers, the first commercially successful method for quantitative control of concentrations of volatile liquid anesthetics delivered to patients.

ANESTH ANALG
1989;68:20–4

Vecuronium Infusion Requirements in Pediatric Patients during Fentanyl–N_2O–O_2 Anesthesia

Olli A. Meretoja, MD

MERETOJA OA. Vecuronium infusion requirements in pediatric patients during fentanyl–N_2O–O_2 anesthesia. Anesth Analg 1989;68:20–4.

Eighty-one pediatric patients, ranging from neonates to adolescents, were studied during fentanyl–N_2O–O_2 anesthesia to determine for each of them the vecuronium infusion required to maintain 90–95% neuromuscular block (NMB). Electromyographic monitoring with train-of-four stimuli was used. The steady infusion rate was 62 ± 15 (SD) $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in neonates and infants. This rate was 40% of that required by children 3 to 10 years old (154 ± 49 $\mu g \cdot kg^{-1} \cdot hr^{-1}$; $P < 0.05$). In adolescents the vecuronium requirement was less than in children and was comparable to that reported in adults in other studies (89 ± 13 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). Despite considerable individual variation, the infusion rate could be reliably estimated on the basis of duration of >90% NMB maintained by small doses of vecuronium given after intubation. Also, a close correlation existed between the duration of >90% NMB maintained by 100 $\mu g/kg$ of vecuronium and the individual infusion rate ($r^2 = 0.76$).

ANESTHESIA—pediatric. NEUROMUSCULAR RELAXANTS—vecuronium.

The neuromuscular effects of bolus doses of vecuronium have been evaluated in infants and children (1–6). After a single dose of vecuronium, spontaneous recovery from the neuromuscular block is slower in infants than in children (1,3). This can be explained by differences in the pharmacokinetics (4) and in the potency (2,6) of vecuronium in different age groups. When vecuronium is used during long-lasting anesthesia, the drug may be given either by intermittent doses or by a continuous infusion, but information is lacking on vecuronium infusion requirements in pediatric patients. The aim of this study was to determine the steady infusion rate of vecuronium needed to maintain 90–95% neuromuscular block in neonate to adolescent pediatric patients during fentanyl–N_2O–O_2 anesthesia.

Methods

Eighty-one ASA physical status I–II patients who were not receiving any medications that affect neuromuscular transmission were selected for the study on the basis of their age and the planned duration of surgery. The study protocol was approved by the Institutional Ethical Committee, and the parents gave informed consent. Nine groups of nine patients each were evaluated: 1) those less than three months old, 2) from three months to less than one year old, 3) from one to less than two years old, 4) from two to less than three years old, 5) from three to less than five years old, 6) from five to less than seven years old, 7) from seven to less than ten years old, 8) from ten to less than 13 years old, and 9) from 13 to less than 17 years old. Patient characteristics are shown in Table 1. Intraoperative blood loss did not exceed 2% of the calculated blood volume in any patient during the study period. Throughout the procedure the patients received 5% dextrose in 60 mmol/L NaCl. The infusion rate was 3–5 $ml \cdot kg^{-1} \cdot hr^{-1}$.

Premedication was prescribed on clinical basis: patients in group 1 received no premedication. Patients in group 2 received rectal methohexital, 15 mg/kg. Patients in groups 3–5 had oral flunitrazepam, 0.08 mg/kg (most often supplemented with rectal methohexital, 10–15 mg/kg). Patients in groups 6–9 had oral flunitrazepam, 0.08 mg/kg (maximum dose 2.0 mg). After glycopyrrolate, 5 $\mu g/kg$ (IV), anesthesia was induced with fentanyl, 3 $\mu g/kg$, and thiopental, 2–4 mg/kg, and maintained with nitrous oxide

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Address correspondence to Dr. Olli Meretoja, Department of Anesthesiology, Children's Hospital, SF-00290 Helsinki, Finland.

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Table 1. Patient Characteristics

Group	Age (years)	Weight (kg)	Body surface area (m^2)
Under 3 months*	0.1 ± 0.1	4.0 ± 0.8	0.23 ± 0.03
3 months to <1 yr	0.5 ± 0.1	8.0 ± 0.8	0.38 ± 0.02
1 yr to <2 yr	1.5 ± 0.3	10.5 ± 1.2	0.47 ± 0.04
2 yr to <3 yr	2.3 ± 0.3	13.5 ± 1.4	0.57 ± 0.03
3 yr to <5 yr	4.2 ± 0.5	18.2 ± 2.5	0.73 ± 0.05
5 yr to <7 yr	5.7 ± 0.5	19.9 ± 3.3	0.80 ± 0.09
7 yr to <10 yr	8.9 ± 0.9	28.7 ± 4.9	1.03 ± 0.11
10 yr to <13 yr	11.9 ± 0.9	39.2 ± 8.2	1.27 ± 0.15
13 yr to <17 yr	14.7 ± 1.1	53.5 ± 8.7	1.57 ± 0.15

Values are expressed as means ± SD.
*Seven patients aged less than one month.

in oxygen 2:1 and incremental doses of 1–2 μg/kg fentanyl. Throughout anesthesia ventilation was controlled to maintain end-tidal carbon dioxide at 5.0–5.5% (infrared analysis by Normocap, Datex, Helsinki, Finland). No volatile anesthetics were used.

Neuromuscular transmission was monitored by electromyography (Relaxograph, Datex, Helsinki, Finland). The stimulating surface electrodes were positioned over the ulnar nerve near the wrist and the recording electrodes were placed over the adductor pollicis muscle in the thenar eminence and over the volar side of the proximal phalanx of the middle finger. The forearm was taped to a dorsal splint to immobilize the hand and the fingers and covered with a transparent light dressing to avoid surface cooling. The neuromuscular monitor was calibrated when the patient was fully asleep and breathing N_2O in O_2, and the evoked electromyographic response to the train-of-four stimuli (at 2 Hz every 20 seconds) was recorded.

When the calibration was adjusted, vecuronium was administered in incremental doses to produce 90–95% neuromuscular block (NMB). Thereafter the tracheal intubation was performed. Subsequent doses of vecuronium (10–15 μg/kg) were administered when the first twitch height in the EMG response was recovered to 10% of the calibration value. The dose of vecuronium and the time elapsed between every administration was recorded. When the time between successive vecuronium doses became unchanged, the infusion was initiated. The individual infusion rate was calculated from the time elapsed between the incremental vecuronium doses: e.g., if after a 15 μg/kg dose of vecuronium the NMB recovered to 90% level at 7 minutes, then the infusion rate was (60 min/7 min) × 15 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ = 130 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (see Fig. 1) (If a = time in minutes elapsed between incremental doses, b = incremental dose in μg/kg, and y = infusion rate in $\mu g \cdot kg^{-1} \cdot hr^{-1}$, then y = (60/a) × b.) The steady state infusion was the rate that maintained an unchanged 90–95% NMB for at least 30 minutes during the first 90 minutes of anesthesia.

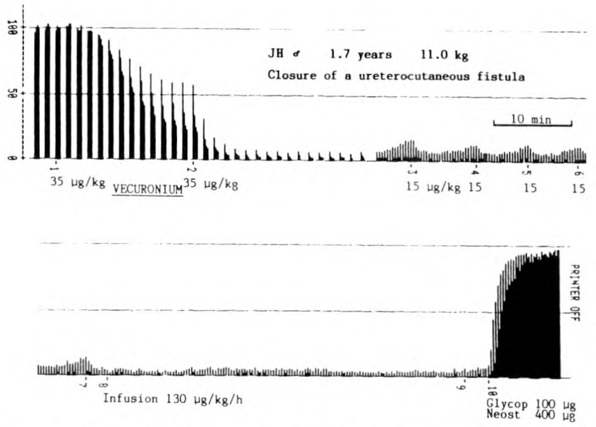

Figure 1. A typical electromyographic tracing from a 1.7-year-old boy. Two doses of vecuronium, 35 μg/kg each, established the initial 94% neuromuscular block. Subsequent vecuronium increments were 15 μg/kg. When an unchanged 7 minute time interval between these increments was established, the IV infusion was initiated. The infusion rate was calculated to be (60 min/7 min) × 15 = 130 $\mu g \cdot kg^{-1} \cdot hr^{-1}$.

The vecuronium infusion rate was calculated in each patient on the basis of both body weight and body surface area. Statistical analysis was performed by analysis of variance (ANOVA), with Welch modification in cases of unequal variances (BMDP Statistical Software 7D, 1987, Berkeley, California). Tukey's Studentized range method was used to compare the steady state vecuronium infusion rates of the different groups. A least-square linear regression analysis (BMDP Statistical Software 6D) was made to establish the correlation between the individual infusion rates and the ED_{95} (calculated by log-probit transformation). $P < 0.05$ was considered statistically significant. The value are expressed as mean ± SD.

Results

Steady vecuronium infusion rates were initiated before the end of the first hour of anesthesia in all patients. On the average, patients needed four incremental doses of vecuronium after intubation and prior to commencement of the infusion. In 73 patients the infusion rate was predicted correctly to maintain the desired 90–95% NMB unchanged. In the remaining eight patients one rate adjustment (19 ± 7% change in the infusion rate) was needed. The mean time elapsed between intubation and the start of the steady infusion rate was 35 ±10 minutes, and the duration of the steady vecuronium infusion averaged 48 ± 24 minutes. The average NMB was 94 ± 2%

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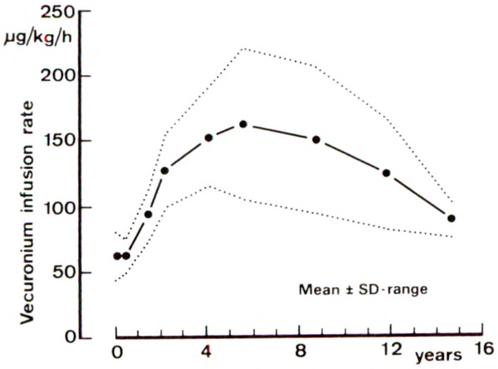

Figure 2. The age-dependence of the steady-state vecuronium infusion rate required to maintain a 90–95% neuromuscular block in pediatric patients during balanced anesthesia.

Table 2. The Infusion Requirement of Vecuronium to Maintain a 90–95% Neuromuscular Block during Fentanyl–N_2O–O_2 Anesthesia

Patient group	Rate ($\mu g \cdot kg^{-1} \cdot hr^{-1}$)	Rate ($\mu g \cdot m^{-2} \cdot hr^{-1}$)
Under 3 months	62 ± 19*	1070 ± 350†
3 months to <1 yr	62 ± 12*	1330 ± 280†
1 yr to <2 yr	94 ± 18‡	2110 ± 470§
2 yr to <3 yr	128 ± 29	2980 ± 620
3 yr to <5 yr	149 ± 33	3690 ± 710
5 yr to <7 yr	162 ± 59	4000 ± 1470
7 yr to <10 yr	150 ± 56	4110 ± 1490
10 yr to <13 yr	124 ± 42	3670 ± 840
13 yr to <17 yr	89 ± 13‡	3020 ± 570

The values are expressed as means ± SD.
*Denotes $P < 0.05$ vs <3, <5, <7, <10, and <13 years.
†Denotes $P < 0.05$ vs <3, <5, <7, <10, <13, and <17 years.
‡Denotes $P < 0.05$ vs <5, <7, and <10 years.
§Denotes $P < 0.05$ vs <5, <7, <10, and <13 years.

during the infusion period, and this was comparable in the nine groups of patients studied (range of mean NMB of the groups was 93–96%).

The vecuronium infusion requirement was clearly dependent on the age of the patient (Fig. 2 and Table 2). In neonates (patients less than 1 month old, $n = 7$) and infants (from 1 month to less than 1 year old, $n = 11$) it was 62 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. This was 40% of the infusion rate of children from 3 to <10 years of age (154 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) ($P < 0.05$). Also the infusion rate of adolescents (89 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) was significantly less than that of children.

By linear regression analysis the following significant correlations were noted: 1) between the individual ED_{95} and the required infusion rate (infusion rate $= 1.8 \times ED_{95} - 5$; $r^2 = 0.48$), 2) between the dose of vecuronium given during the first 30 minutes after intubation and the infusion rate (infusion rate = 1.9 × given dose + 5; $r^2 = 0.91$), and 3) between the total dose of vecuronium administered during the first 30 minutes of anesthesia and the infusion rate (infusion rate = 1.3 × total dose − 30; $r^2 = 0.80$). Furthermore, a close correlation existed between the time of >90% NMB maintained by cumulative 100 μg/kg dose of vecuronium and the individual infusion rate ($\log_e$(infusion rate) = 5.30 − 0.02 × duration of >90% NMB; $r^2 = 0.76$) (Fig. 3).

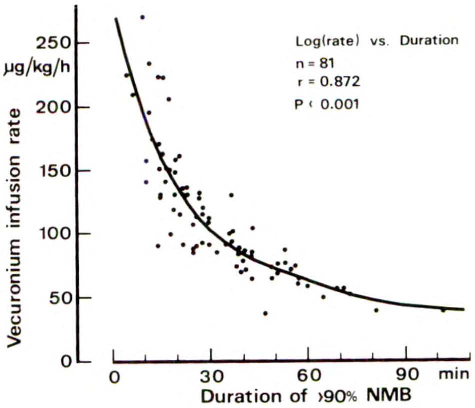

Figure 3. The relationship between the duration of >90% neuromuscular block maintained by the cumulative 100 μg/kg dose of vecuronium, and the individual vecuronium infusion requirement. The longer vecuronium maintained the >90% NMB, the smaller was the required infusion rate. If the duration of >90% NMB is 20, 40, or 60 minutes, then the estimated infusion rate is 136, 84, or 63 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, respectively. The regression line is a fourth-degree polynomial function.

Discussion

The present study shows that the infusion rate of vecuronium to maintain a 90–95% NMB during balanced anesthesia is significantly dependent on the age of the pediatric patient. Infants required lesser rates (62 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) than children (154 $\mu g \cdot kg^{-1} \cdot hr^{-1}$), and the requirements of adolescents approached that of adults. In adult studies, a fairly common infusion rate of 70–80 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ (approximately 1.5 times the ED_{95} per hour) is needed to maintain an unchanged 90% NMB during balanced anesthesia (7–10).

The present method for calculating individual vecuronium requirements was based on the time required in each patient to establish and maintain >90% NMB using small incremental doses of vecuronium. With this method the estimated infusion rate could be predicted accurately in 90% of patients. After the establishment of the initial 95% NMB it took 7.5 ± 2.6 minutes before the EMG twitch height recovered to 10% of the calibration value. Thereafter, the duration of >90% NMB maintained by the first vecuronium increment was 7.0 ± 2.8 minutes compared to the duration of 8.9 ± 3.4 minutes maintained by the last increment before the steady infusion was initiated. Consequently, if the infusion was started after the first vecuronium increment, the infusion rate would have been overestimated. The first increments were most probably needed to saturate the total volume of distribution, whereas the last increments and the steady state infusion replaced the amount of vecuronium that was eliminated.

The elimination of drugs at steady state is the product of drug clearance and plasma concentration. Fisher et al. used mechanomyography and measured clearance and plasma concentration of vecuronium at 50% neuromuscular block during halothane anesthesia in five infants (3–11 months old), five children (20–59 months old), and five adults (4). When calculated from their data, the amount of vecuronium eliminated at steady 50% neuromuscular block during halothane anesthesia was 19, 39, and 29 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in infants, children and adults, respectively. When these figures are compared to our infusion rates of 62, 130, and 89 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in comparable age groups (the last figure is for adolescents), ratios are 1:3.3, 1: 3,3, and 1:3.1, respectively. These ratios seem to be theoretically correct, because previously it has been determined that the dose–response curves of vecuronium are parallel in all age groups of pediatric patients with a slope of 6.7 probits/log (6). This slope means that an increase in the intensity of the NMB from 50% to 95% occurs with a 1.8-fold increase in the dose of vecuronium. Furthermore, during balanced anesthesia the vecuronium requirement is 1.3–1.7 times the requirement during halothane anesthesia (2,6,9). Finally, the degree of NMB reflected by electromyography is less than that reflected by mechanomyography (11). Consequently, the present data and the results of Fisher et al. (4) correlate well with each other, although the studies were totally different.

In the present study, the first intermittent vecuronium doses were given as small increments to make it possible to calculate the exact vecuronium requirement from the beginning of anesthesia until the cessation of infusion at the end of the study. It was thus also possible to determine the best clinical method for estimating in an individual patient the steady state infusion rate necessary to maintain the desired 90–95% NMB. The correlation between the individual ED_{95} and the infusion rate showed great variability ($r^2 = 0.48$) and, therefore, ED_{95} seems not to be an optimal guide for estimating the steady infusion rate. In neonates and infants, the infusion rate was 1.3 ± 0.3 times the individual ED_{95} per hour as compared to 1.8 ± 0.5 times the individual ED_{95} per hour in older patients.

The total amount of vecuronium required to maintain the NMB between 90–98% during the first 30 minutes of anesthesia showed excellent correlation with the steady state infusion requirement and only a fairly small individual variation ($r^2 = 0.80$). The dose needed during the 30 minutes after establishment of 90–95% NMB showed even better correlation ($r^2 = 0.91$). Thus, either of these two findings could form the basis for a satisfactory method of calculating the vecuronium infusion rate needed to maintain a 90–95% NMB. An additional method probably could be based on the finding of close correlation between the individual infusion rate and the duration of >90% NMB maintained by 100 μg/kg of vecuronium (Fig. 3): the correlation curve shows that a duration of 20 minutes is associated with an estimated infusion requirement of 136 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, whereas a duration of 40 min is related to an 84 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ infusion rate.

The described principles for estimating the required individual infusion rate of vecuronium may be used even if electromyography or mechanomyography are not available. When a peripheral neurostimulator with train-of-four stimuli is used, incremental doses of vecuronium may be given when two or three twitch responses are detected. If the time intervals between these increments are calculated, then estimation of the infusion rate may be made by the procedure described in Methods. The infusion rate can also be calculated on the basis of the dose needed during the 30 minutes after intubation, as shown above. If intermediate-acting neuromuscular blocking agents are used during long-lasting anesthesia both of these estimations are clinically easy to use.

The range of steady state vecuronium infusion requirement was 37–270 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in the present study. Therefore, the infusion method cannot be used accurately with vecuronium if the infusion is initiated using the same rate of infusion in all patients. The average variance of the infusion rate (SD divided by mean infusion rate) in our study groups was 26%, which is of the same order as found in adults (8,9), and also of the same order as found with atracurium in pediatric patients (12). The age-dependency of the steady state infusion requirement of vecuronium is, however, not like that seen with atracurium (12,13).

In conclusion, the present study shows that the infusion requirement of vecuronium to maintain a steady state 90–95% NMB during balanced anesthesia in pediatric patients depends significantly on the age of the patient. Neonates and infants require the lowest infusion rate, children between 3 and 10 years need the highest rate, and adolescents need a rate identical to that required by adults and close to the infant value. The individual infusion rates needed can be accurately determined from the evolution of NMB after small incremental doses of vecuronium. The duration of NMB maintained by constant vecuronium dose may also reliably estimate the final infusion requirement.

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ANESTH ANALG
1989;68:25–31

Thromboxane Mediation of Pulmonary Hemodynamic Responses after Neutralization of Heparin by Protamine in Pigs

Peter F. Conzen, MD, Helmut Habazettl, MD, Ralph Gutmann, Jonny Hobbhahn, MD, Alwin E. Goetz, MD, Klaus Peter, MD, and Walter Brendel, MD

CONZEN PF, HABAZETTL H, GUTMANN R, HOBBHAHN J, GOETZ AE, PETER K, BRENDEL W. Thromboxane mediation of pulmonary hemodynamic responses after neutralization of heparin by protamine in dogs. Anesth Analg 1988;68:25–31.

Protamine neutralization of heparin is often associated with severe hemodynamic side-effects, including pulmonary hypertension and systemic hypotension. Because prostanoids may be involved, the authors studied the role of arachidonic acid metabolites, especially thromboxane A_2, in this process. During anesthesia with enflurane and fentanyl, four groups of pigs were studied: Group 1 (n = 10) received heparin (250 IU/kg), followed by protamine (100 mg) after 15 minutes to neutralize the heparin. The same protocol was used in group 2 (n = 11), except that the thromboxane A_2 receptor antagonist BM 13.177 (10 mg/kg) was infused 5 minutes before the protamine. The protocol for group 1 was also used for group 3 (n = 7) except that these animals were pretreated with indomethacin (10 mg/kg). Animals in group 4 (n = 10) were given protamine only (100 mg). Pulmonary artery pressure and pulmonary vascular resistance increased significantly in group 1 after protamine neutralization of heparin. This was accompanied by significant increases in plasma concentrations of the cyclooxygenase products thromboxane B_2, 6-keto-prostaglandin $F_{1\alpha}$, and prostaglandin $F_{2\alpha}$. Cyclooxygenase products increased to comparable degrees in group 2, but without hemodynamic effects. Leukocyte counts decreased comparably in both groups. Hemodynamic reactions, as well as changes in plasma prostanoid levels were absent in group 3, and group 4, but leukocyte counts were less affected in animals that received protamine alone. The results indicate that the hemodynamic side-effects of protamine are mediated by prostanoids and that thromboxane A_2 release is the pivotal step, because side effects were effectively prevented by pretreatment with a thromboxane receptor antagonist. Leukocyte or platelet counts were not directly related to the severity of hemodynamic alterations.

Key Words: BLOOD, COAGULATION—protamine, heparin. HORMONES—prostaglandins, thromboxane.

Protamine sulfate may be associated with adverse hemodynamic side effects when administered to neutralize the anticoagulant effects of heparin. These side effects include pulmonary hypertension and systemic hypotension (1,2).

Thromboxane A_2, the predominant cyclooxygenase product of arachidonic acid in platelets and a potent vasoconstrictor and stimulus of platelet aggregation (3), could be responsible for these hemodynamic responses, especially the pulmonary hemodynamic side effects of protamine. Two recent studies reported activation of cyclooxygenase cascade with markedly increased plasma levels of its metabolites thromboxane A_2 and prostacyclin after protamine administration in man. Morel et al., for example, in a prospective study of 48 patients (4) identified three subjects with acute pulmonary hypertension and a considerable elevation of plasma prostanoid concentrations after protamine given to heparinized patients. These authors thereby confirmed an earlier case report where similar findings were described (5).

Increased plasma concentrations of prostanoids were also obtained in sheep (6), as well as in pigs (7), where plasma metabolites of thromboxane A_2 (6,7) and prostacyclin (7) increased significantly after protamine neutralization of heparin. Even more important, in both studies, the hemodynamic side reactions were effectively prevented with the cyclooxygenase inhibitor indomethacin.

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Address correspondence to Dr. Conzen, Institute of Surgical Research, Ludwig-Maximilians-University, Marchioninistr. 15, 8000 Munich 70, Bavaria, Federal Republic of Germany.

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Protamine has also been described as affecting white blood cell and platelet counts (1,8). Marked reductions of leukocyte (9,10) and platelet (11,12) counts have been reported. The significance of these changes in terms of observed hemodynamic reactions is not completely understood: some authors report decreases of platelet counts after protamine and ascribe the hemodynamic alterations to the release of a smooth muscle contracting substance from platelet aggregates (12,13). Others found that similar decreases in leukocyte and platelet counts were not necessarily associated with hemodynamic reactions (4).

Thus, the purpose of the current study was twofold: 1) to further assess the role of thromboxane A_2 in the hemodynamic side effects of protamine when given to neutralize heparin, as well as to investigate a potential means of minimizing such effects; and 2) to assess platelet and leukocyte kinetics associated with protamine administration and their relationship to the arachidonic acid cascade.

Methods

Anesthesia and Surgical Preparation

Upon approval by the animal care committee, experiments were performed in 38 pigs of either sex with an average body weight of 30.5 kg (range 25–34 kg). Anesthesia was induced by IM ketamine, 10 mg/kg, flunitrazepam, 0.1 mg/kg, and atropine 0.5 mg. The animals were tracheotomized and the lungs ventilated mechanically (Servo-Ventilator 900 B, Siemens AG, West Germany) using a mixture of O_2 and N_2O to maintain arterial Po_2 at 100 mm Hg. The tidal volume was set to maintain end-expiratory CO_2 at 4.5 vol%. Positive end expiratory pressure of 3 cm H_2O prevented atelectasis. Adequate anesthetic depth was maintained by enflurane (0.5–0.7 vol%) and fentanyl ($0.1\ mg \cdot kg^{-1} \cdot hr^{-1}$).

Monitoring of hemodynamic parameters and sampling of blood required two large bore polyethylene catheters in the abdominal aorta (for monitoring arterial pressure and for blood sampling) and in the inferior vena cava (for infusion of balanced electrolyte solutions), placed through the femoral vessels. Two flotation directed, balloon-tipped catheters of different sizes were placed in the pulmonary artery through external jugular veins: the 5-French catheter served for determination of cardiac output (Cardiac Output Computer 9530, Mansfield Inc., Mansfield, MA), the 7-French catheter for measurement of pulmonary artery pressure and for blood sampling. A high-fidelity catheter tip-manometer (Millar Instruments, Houston, TX) advanced to the left ventricle through a carotid artery measured left ventricular pressure. Systemic and pulmonary vascular resistances were derived from, respectively, the aortic to right atrial and the pulmonary artery to left ventricular end-diastolic pressure-gradients and from cardiac output.

Laboratory Analyses

Blood-gas tensions in anaerobically collected blood samples were detected by an ABL 300 (Radiometer, Copenhagen, Denmark). White blood cell counts were measured using a coulter counter (Model T540, Coulter Electronics, Krefeld, West Germany). Platelet counts were made in a counting chamber by means of a light microscope at a magnification of ×500.

For determination of plasma prostanoid levels, 3 ml of blood were collected from the abdominal aorta and the pulmonary artery using precooled plastic syringes. The syringes contained 0.1 ml indomethacin (1 mg/ml) and 0.2 ml sodium EDTA (77 mM). The blood was centrifuged immediately at 4°C and the plasma stored at −70°C until analyzed by radioimmunoassays in unextracted plasma for thromboxane A_2 and prostacyclin by their stable degradation products thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ respectively, and for prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). The major degradation product of $PGF_{2\alpha}$, $KH_2PGF_{2\alpha}$, was measured as well. Dextran-coated charcoal was used to separate free from antibody-bound antigen fractions and all determinations were performed in duplicate. Antibodies came from Pasteur Diagnostics, Paris.

Experimental Protocol

Baseline recordings of hemodynamic parameters and blood samples were obtained from all animals 1 hour after surgical preparations and with stable hemodynamic conditions (t_0). The animals were randomly assigned to four experimental groups.

Group 1 animals (n = 10) received heparin (250 IU/kg) intravenously and recordings were repeated after 5 (t_1) and 15 (t_2) minutes. This was followed by infusion of protamine sulfate (100 mg) over 2 minutes. Data were again recorded at 2 (t_3), 5 (t_4), and 15 (t_5) minutes after the end of the infusion. The manufacturer of the protamine (Novo Industrie, Mainz, West Germany) states that 10–15 mg protamine are

Table 1. Hemodynamic Variables in the Animals of Group 1 (Untreated Controls)*

	t_0	t_1	t_2	t_3	t_4	t_5
HR (beats/min)	82 ± 4	81 ± 4	81 ± 4	91 ± 5†	89 ± 4	91 ± 6
MAP (mmHg)	89 ± 3	89 ± 3	91 ± 3	87 ± 5	81 ± 4†‡	83 ± 4
MPAP (mmHg)	17 ± 1	18 ± 2	20 ± 2	33 ± 3†‡	27 ± 2†	21 ± 2
CO (L/min)	3.5 ± 0.2	3.4 ± 0.2	3.5 ± 0.1	3.6 ± 0.2	3.7 ± 0.2	3.6 ± 0.1
SVR (dynes·sec·cm^{-5})	2011 ± 130	2072 ± 160	2060 ± 140	1999 ± 130	1735 ± 100	1816 ± 140
PVR (dynes·sec·cm^{-5})	172 ± 28	184 ± 38	204 ± 37	527 ± 81†‡	399 ± 75†	255 ± 70
LVEDP (mmHg)	10 ± 1	10 ± 1	11 ± 1	9 ± 1	9 ± 1	10 ± 1
SV (ml)	43 ± 3	44 ± 3	44 ± 3	41 ± 3	43 ± 2	42 ± 2

Abbreviations: HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LVEDP, left ventricular end-diastolic pressure; SV, stroke volume.

*Results are given as mean ± SEM before (t_0) and after (t_1) heparin, before protamine (t_2), and 2 (t_3), 5 (t_4) and 15 (t_5) minutes after end of protamine infusion.

†$P < 0.05$ versus corresponding time in group 2 (thromboxane antagonist).

‡$P < 0.05$ versus t_2 (immediately before protamine).

required to neutralize 1000 IU heparin. We therefore assume that the heparin effects were completely neutralized in all animals. The solvent of the TX-antagonist BM 13.177 (trometamol, 1.25 mg) was infused as a placebo 5 minutes prior to t_2.

Group 2 animals ($n = 11$) received heparin as in group 1. This was followed by IV infusion of the thromboxane receptor antagonist BM 13.177 (10 mg/kg; Boehringer Mannheim, West Germany) 5 minutes before heparin neutralization by protamine. Recordings were obtained as in group 1 (t_0–t_5).

Group 3 animals ($n = 7$) were pretreated by indomethacin (10 mg/kg IV) to completely block cyclooxygenase as soon as a central venous catheter had been placed. The experimental protocol was thereafter the same as in group 1.

Group 4 (n = 10) received protamine (100 mg) without a preceding infusion of heparin. Recordings were made immediately before protamine (t_2) and 2, 5, and 15 minutes (t_3–t_5) after completion of the infusion.

Statistical Analyses

Statistical comparisons within groups were performed by the Friedman rank-analysis of variance. This was followed by Wilcoxon and Wilcox multiple comparisons to determine when experimental results differed significantly from baseline values before protamine (t_2). Comparisons between groups 1–4 at corresponding experimental steps were performed by Kruskal–Wallis analysis followed by appropriate single comparisons. A P value smaller than 0.05 was considered statistically significant. All results are expressed as means ± SEM.

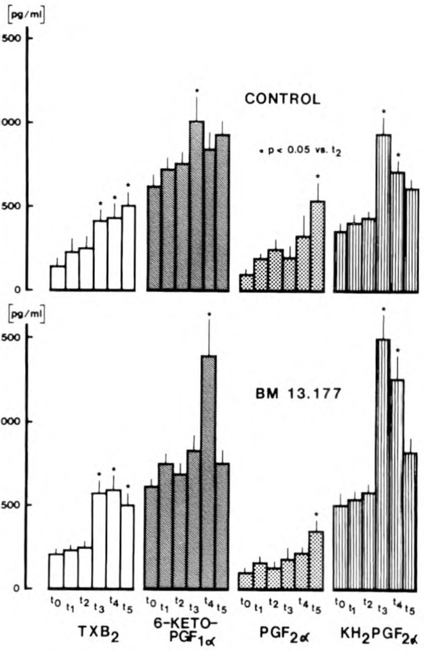

Figure 1. Plasma prostanoid concentrations in group 1 (control, upper part) and group 2 (thromboxane receptor antagonist BM 13.177, lower part). All values given as mean ± SEM. Abbreviations: TXB_2, thromboxane B_2; 6-keto-$PGF_{1\alpha}$, stable metabolite of prostacyclin; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; $KH_2PGF_{2\alpha}$, metabolite of prostaglandin $F_{2\alpha}$. Results are given before (t_0) and after (t_1) heparin, before protamine (t_2), and 2 (t_3), 5 (t_4), and 15 (t_5) minutes after end of protamine infusion.

Results

Untreated Animals, Group 1

The infusion of heparin did not affect systemic hemodynamics (Table 1). Also, prostanoid concentrations and blood cell counts were unchanged by heparin (Fig. 1, Table 2).

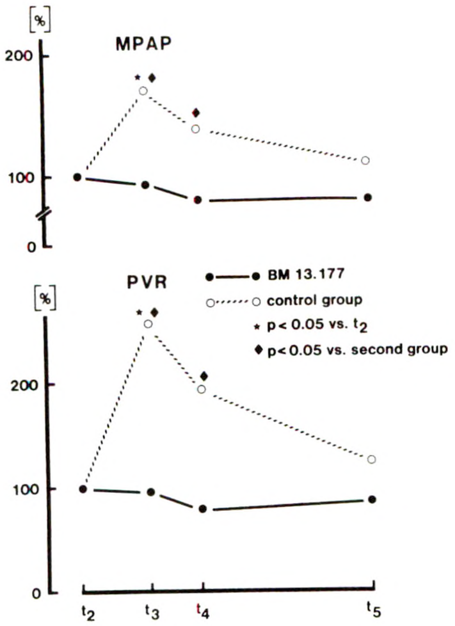

Figure 2. Changes in mean pulmonary artery pressure (MPAP) and pulmonary vascular resistance (PVR) in group 1 (control) and in group 2 (BM 13.177). The control value immediately before protamine infusion (t_2) was set 100%; results are also given at 2 (t_3), 5 (t_4), and 15 (t_5) minutes after termination of protamine infusion.

Neutralization of heparin by protamine produced significant pulmonary vasoconstriction: mean pulmonary artery pressure increased by approximately 65%, pulmonary vascular resistance by 158% 2 minutes after protamine (Fig. 2). This was followed by a slight but significant 11% decrease in mean arterial pressure at t_4. Heart rate remained essentially unchanged (Table 1).

Systemic arterial and mixed venous plasma concentrations of thromboxane B_2 (TXB_2) and 6-keto-$PGF_{1\alpha}$ increased significantly as soon as 2 minutes after the infusion of protamine had been completed (Fig. 1). Arterial plasma concentrations of TXB_2 and $PGF_{2\alpha}$ were still significantly elevated at 15 minutes after protamine (t_5). No significant differences were detected between arterial and mixed-venous plasma samples.

Arterial leukocyte counts decreased significantly after protamine in group 1 at t_3 and t_4 (Table 2). Differential blood counts revealed that all subpopulations of leukocytes decreased in number, although polymorphonuclear-neutrophil leukocytes (PMNL) decreased more than lymphocytes. Platelet counts remained essentially unchanged.

Thromboxane Antagonist Treated Animals, Group 2

Infusion of the thromboxane receptor antagonist was not followed by detectable changes in hemodynamics, blood-gas tensions, or plasma levels of arachidonic acid metabolites. Systemic hemodynamics remained unchanged in the animals given BM 13.177 before protamine. No evidence of pulmonary vasoconstriction or systemic hypotension was detected. Pulmonary vascular resistance even decreased slightly (−21%) 5 minutes (t_4) after completion of protamine infusion (Table 3). Changes in mean arterial pressure, mean pulmonary artery pressure, and pulmonary vascular resistance were significantly different in groups 1 and 2 after protamine at t_3 and t_4.

Although hemodynamic alterations were absent, changes in plasma prostanoid concentrations were slightly more pronounced in group 2 than in group 1. This involved TXB_2 (+112% vs +101%), as well as $PGF_{2\alpha}$ (+102% vs +63%) at t_3. However, because of interindividual variability, no statistically significant differences were detected when compared with the untreated animals. Protamine caused a significant 66% decrease of leukocyte counts, whereas platelet counts remained unchanged (−3%), i.e., not statistically significantly different from group 1. Leukocyte counts, however, decreased significantly more than in the animals of group 4, which received protamine alone (Table 2).

Indomethacin Pretreated Animals, Group 3

No changes in hemodynamics or in plasma prostanoid concentrations occurred after protamine infusion in animals pretreated with indomethacin. Mean peripheral arterial pressure and mean pulmonary artery pressure remained at their baseline values of 90 mm Hg and 21 mm Hg throughout the study. Leukocyte counts decreased as in groups 1 and 2. In contrast, however, platelet counts decreased significantly at 2 and 5 minutes after protamine (t_3, t_4). This does not necessarily indicate a true difference compared to the other groups but rather is due to more uniform reactions in these animals.

Protamine Alone, Group 4

As in group 3, neither mean arterial or mean pulmonary artery pressures nor prostaglandin concentrations changed in these animals. Platelet counts were not affected by protamine infusion. Leukocyte counts, however, decreased significantly from an average of 11430 cells/mm^3 to 8140 cells/cm^3 at t_3. This decrease in leukocyte counts was significantly less than in groups 1–3 (Table 2).

Table 2. Leukocyte and Platelet Counts in Arterial Blood Samples*

	t_0	t_1	t_2	t_3	t_4	t_5
Leukocyte (cells/mm^3)						
Group 1	13682 ± 1401	13818 ± 1151	13827 ± 1258	7400 ± 946†‡	8600 ± 1044†	13300 ± 1441
Group 2	13800 ± 1340	14400 ± 1336	16040 ± 1311	7120 ± 754†‡	9950 ± 869†	14510 ± 1242
Group 3	11780 ± 1332	10720 ± 1198	12040 ± 1255	6040 ± 1023†‡	7440 ± 899†	9660 ± 960
Group 4	—	—	11430 ± 848	8140 ± 753†	8740 ± 888†	9810 ± 981
Platelets (10^3 cells/mm^3)						
Group 1	381 ± 44	357 ± 37	374 ± 41	355 ± 40	314 ± 28	331 ± 35
Group 2	432 ± 28	408 ± 31	398 ± 23	386 ± 31	385 ± 38	376 ± 31
Group 3	387 ± 24	403 ± 11	407 ± 24	344 ± 22†	368 ± 28	351 ± 28
Group 4	—	—	396 ± 31	397 ± 28	397 ± 34	407 ± 30

*Group 1, untreated controls; group 2, BM 13.177 (10 mg/kg 5 minutes prior to protamine); group 3, indomethacin pretreated animals; group 4, protamine alone. Results are given as mean ± SEM before (t_0) and after (t_1) heparin, before protamine (t_2), and 2 (t_3), 5 (t_4) and 15 (t_5) minutes after end of protamine infusion.

†$P < 0.05$ vs t_2 in the same group.

‡$P < 0.05$ vs corresponding step in group 4.

Table 3. Systemic Hemodynamic Variables in the Pretreated* Animals of Group 2

	t_0	t_1	t_2	t_3	t_4	t_5
HR (beats/min)	85 ± 4	83 ± 4	77 ± 3	78 ± 3†[b]	77 ± 2	78 ± 4
MAP (mmHg)	87 ± 3	88 ± 3	96 ± 4	93 ± 4	92 ± 5†	91 ± 5
MPAP (mmHg)	20 ± 1	20 ± 1	20 ± 1	19 ± 1†	17 ± 1†	17 ± 1
CO (L/min)	3.7 ± 0.2	3.6 ± 0.2	3.4 ± 0.2	3.4 ± 0.1	3.4 ± 0.1	3.2 ± 0.2
SVR (dynes·sec·cm^{-5})	1887 ± 150	1907 ± 140	2288 ± 200	2186 ± 180	2184 ± 140	2250 ± 150
PVR (dynes·sec·cm^{-5})	218 ± 39	204 ± 38	198 ± 29	194 ± 24†	156 ± 21†	168 ± 22
LVEDP (mmHg)	11 ± 1	11 ± 1	11 ± 1	12 ± 1	11 ± 1	12 ± 1
SV (ml)	44 ± 2	45 ± 2	44 ± 3	44 ± 2	46 ± 3	44 ± 3

All results are given as mean ± SEM. For abbreviations see Table 1.

*BM 13.177; 10 mg/kg prior to protamine

†$P < 0.05$ versus corresponding step in group 1 (untreated controls).

Discussion

The results of this study indicate two main points. 1) Thromboxane A_2 largely mediates the adverse pulmonary hemodynamic effects after protamine antagonization of heparin. Both the significantly increased plasma concentrations of this arachidonic acid metabolite and the inhibition of hemodynamic side reactions after pretreatment with the thromboxane receptor antagonist BM 13.177 support this conclusion. 2) The hemodynamic alterations after protamine are not directly related to changes in leukocyte or platelet counts since these may vary independently of the hemodynamic parameters.

The general hemodynamic events after protamine administration in this study agree well with a number of observations obtained in patients (4,14) and animals (7,15). The first step (at least when protamine is given intravenously) is pulmonary vasoconstriction, evidenced by increases in pulmonary vascular resistance and in pulmonary artery pressure. Pulmonary vasoconstriction precedes the decrease in arterial pressure. Pronounced increases in plasma concentrations of arachidonic acid metabolites were detected for thromboxane B_2 and 6-keto-$PGF_{1\alpha}$ in group 1. The relevance of arachidonic acid metabolites for the hemodynamic reactions after protamine administration is seen in the results from group 3, where—as in an earlier study from this laboratory (7)—hemodynamic as well as prostanoid changes were absent.

The results obtained in the animals of the second group indicate that the hemodynamic effects observed when heparin is neutralized by protamine are largely mediated by the arachidonic acid metabolite thromboxane A_2. This conclusion is derived from the application of the thromboxane A_2 receptor antagonist BM 13.177, which effectively prevented pulmonary vasoconstriction. The second prostanoid with vasoconstricting properties determined, prostaglandin $F_{2\alpha}$ and its metabolite, $KH_2PGF_{2\alpha}$, were also increased after protamine. But apparently this increase was without hemodynamic consequences. Two possibilities may account for this: first, the increase in $PGF_{2\alpha}$ was too weak to induce hemodynamic effects; second, and more likely, BM 13.177 is not completely specific for the TXA_2 receptor and also blocks the $PGF_{2\alpha}$ receptor. In fact, a crossreactivity of

BM 13.177 with the $PGF_{2\alpha}$ receptor has been demonstrated in vitro (16). We assume that the slight decreases of pulmonary artery pressure and pulmonary vascular resistance in group 2 at t_4 are caused by prostacyclin, as indicated by significantly increased levels of its stable metabolite 6-keto-$PGF_{1\alpha}$ and by absence of this reaction in the cyclooxygenase blocked animals of group 3.

The contribution of arachidonic acid products of the cyclooxygenase pathway to the hemodynamic side reactions after protamine administration was recognized several years ago (17,18). Significantly increased thromboxane B_2 levels after heparin/protamine administration in an awake sheep preparation were reported recently (6). This finding was accompanied by complement activation via the classical pathway and by severe pulmonary hypertension. Pretreatment with a thromboxane synthetase inhibitor reduced the pulmonary hypertensive response, but inhibition was not complete. Although there is no final explanation at present for the different potencies of a thromboxane synthetase inhibitor and a receptor antagonist to inhibit the hemodynamic side effects, the results of this study support our findings that thromboxane A_2 is the key metabolite for this reaction.

Pulmonary vasoconstriction has also been associated with markedly increased plasma thromboxane B_2 levels after protamine administration in humans (4,5). In both studies, the pronounced hemodynamic reactions were accompanied by increased levels of the prostacyclin metabolite 6-keto-$PGF_{1\alpha}$. This finding implies that the same hemodynamic and mediator changes measured in our recent and in previous animal studies (6,7) are related to the same adverse physiologic responses observed in humans (4,5). Such a conclusion suggests that the beneficial effects of thromboxane inhibition might be reproduced in man. A possible limitation—at least after cardiac surgery—is that thromboxane inhibitors potentially aggravate the hemorrhagic tendency after cardiopulmonary bypass (19).

Influences of protamine alone on hemodynamic parameters and prostanoid levels were studied in the animals of the fourth group. Absence of hemodynamic side effects after protamine without preceding infusion of heparin is in good agreement with previous studies in pigs (15). In several earlier experiments conducted in dogs, protamine infusion by itself led to a decrease in arterial pressure (12,20) and even increased levels of plasma thromboxane (18). It was also reported that protamine, when rapidly injected intravenously, was toxic to dogs in doses of 5 mg/kg. However, at this dosage it showed little toxicity in cats, rabbits, and guinea-pigs (8). It therefore appears that the hemodynamic alterations observed in dogs represent species differences and are possibly caused by allergic reactions. Natural protamine antibodies that have recently been described, at least in humans, might support this hypothesis (21).

Although blood cell counts were made in several animals studies and also in man, the precise role of blood elements is poorly defined. Significant thrombocytopenia and leukocytopenia associated with protamine administration were already reported in 1949 (8). It was also noted that experimentally induced thrombocytopenia prevented the subsequent blood pressure drop after protamine, and it was assumed that platelets were required for this response (8,22). However, platelets were not necessary for the pulmonary artery pressure gain in isolated, dextran-perfused cat lungs albeit the pulmonary artery pressure response was greater if the perfusion circuit was primed with blood (23). Pretreatment with acetylsalicylic acid (17) or with indomethacin (this study) blunted the increase in pulmonary vascular resistance, but did not prevent a decrease in platelet counts. In contrast, platelet counts were not affected significantly in the unpretreated animals of group 1 in spite of marked hemodynamic reactions. It therefore appears that, although thrombocytes may be required for the adverse hemodynamic side effects of protamine, there is no close correlation of changes in platelet counts with the severity of the reactions.

The infusion of protamine alone (group 4) decreased leukocyte counts by 29%, significantly less than in combination with heparin. This indicates that although protamine markedly reduces leukocyte counts by itself, this reduction is exaggerated if protamine is given for heparin neutralization. Comparable findings were obtained in another study where protamine and heparin effects on blood cell elements were studied in goats (9). Radioactive labelling in this and another study (24) provided evidence that cells were largely trapped in lung and liver.

White cell counts decreased by approximately 50% in all animals of this study given protamine after heparin. Thus, the leukocytes apparently were not directly involved in the severity of the hemodynamic effects observed and a "mechanical obstruction" of the pulmonary microvasculature as an explanation for the increased vascular resistance can be excluded. However, adherence of leukocytes to the vascular endothelium could initiate the metabolism of arachidonic acid in the presence of heparin/protamine, resulting in synthesis and release of thromboxane A_2 and vasoconstriction. This might account predominately for the pulmonary vascular bed after intravenous injection of protamine, because transpulmonary sequestration of leukocytes, as well as an intrapulmonary activation of the arachidonic acid cascade have been reported (6,7).

In conclusion, the results stress the significance of thromboxane A_2 as the predominant mediator of the adverse hemodynamic reactions after heparin antagonization by protamine. Although the incidence of severe hemodynamic reactions may be much smaller in humans than in experimental animals, selective thromboxane inhibitors currently becoming available for use in man might prove valuable for preventing serious hemodynamic disturbances after protamine.

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Paravertebral Somatic Nerve Block: A Clinical, Radiographic, and Computed Tomographic Study in Chronic Pain Patients

G. Purcell-Jones, BSc (Hon), MRCP, FFARCS, C. E. Pither, MBBS, FFARCS, and
D. M. Justins, MBBS, FFARCS

PURCELL-JONES G, PITHER CE, JUSTINS DM. Paravertebral somatic nerve block: a clinical, radiographic and computed tomographic study in chronic pain patients. Anesth Analg 1989;68:32–9.

The spread of solution after a standardized paravertebral injection was studied to determine the precision and predictability of paravertebral spread. The spread of 5 ml of a solution of radiological contrast medium (sodium iothalamate) and local anesthetic mixture after 45 (34 thoracic, 11 lumbar) paravertebral injections was studied in 31 patients by radiography and computed tomography and correlated with the clinical effects. Spread confined to the paravertebral area occurred after only eight (18%) injections. Spread was epidural after 31 (70%) injections and exclusively so in 14 (31%) injections. Mean sensory loss was greater after epidural spread, but a wide range of sensation loss was observed with all patterns of spread. Intrapleural spread occurred after three injections, as did spread into the psoas muscle. In addition, measurements were made of 114 paravertebral spaces in 20 patients by means of computed tomography. Dimensional factors identified as possibly leading to complications of a paravertebral injection included narrow width of the thoracic transverse processes (mean, 3.18 cm; range, 2.1–4.2 cm) and the wide range in paravertebral dimensions. The distance from bony landmarks to pleura frequently fell outside the limits recommended by many standard texts. We conclude that the spread of a small volume of solution after paravertebral injection is imprecise and unpredictable. Neurolytic and diagnostic paravertebral injections performed without the aid of radiological imaging and contrast media should be regarded as hazardous and interpreted with extreme caution.

Key Words: ANESTHETIC TECHNIQUES—regional, paravertebral. ANESTHETICS, LOCAL—bupivacaine.

Various techniques of paravertebral somatic nerve block have been described (1–9), but little consideration has been given to the subsequent spread of injected solution. Suggested methods for identifying the paravertebral space include positioning the needle either with radiological guidance or blindly according to anatomical landmarks. The latter method has been refined by using the loss of resistance noted on passing through the costotransverse ligament to indicate entry into the paravertebral space (9).

The efficacy of these techniques for relief of postoperative thoraco-abdominal pain is undoubted. Indeed, a single paravertebral injection can produce somatosensory blockade of several nerve roots (9–11). However, the distribution of the injected local anesthetic is uncertain. Paravertebral spread of solution has been demonstrated in a small number of patients by injecting radiographic contrast into a catheter, the tip of which lay in the paravertebral space (11). However, this was preceded by the injection of large volumes of local anesthetic solution (20–30 ml), which may have disrupted anatomical planes. The spread of small volumes of solution, such as those used for diagnostic blocks, has not been investigated. The need for such a study is prompted by reports such as one suggesting the use of paravertebral somatic nerve block as a precise diagnostic test for genitofemoral neuralgia with a view to nerve excision (12). Another study has recommended this procedure as a simple, safe method of performing permanent accurate neurolytic blocks while at the same time describing the widespread analgesic effects of a single injection (9).

Using a standardized technique, we injected a

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Address correspondence to Dr. Justins, Department of Anaesthetics, St. Thomas' Hospital, Lambeth Palace Road, London, SE1 7EH.

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small volume (5 ml) of local anesthetic/radiographic contrast medium mixture into the paravertebral space and studied the spread by radiography and computerized tomography. The clinical effects were correlated with the different types of radiographic spread observed. In addition, the dimensions of the paravertebral space, in relation to recognized landmarks, were measured using computed tomography (CT).

Patients and Methods

Spread of Solution—Clinical and Radiographic Assessment

Hospital ethical committee approval was obtained before commencing the study. The patients had been referred to the pain clinic with a variety of conditions. None of the patients studied had spinal, paravertebral, or pleural pathology, nor had they undergone recent surgical procedures on the thoraco-abdominal region. Forty-five paravertebral injections (34 thoracic and 11 lumbar) were performed in 31 patients as the initial part of a treatment program. Repeated injections were performed in 12 cases. The procedure was explained to the patient and verbal consent was obtained in order to proceed with the additional radiological investigations. The patients lay prone and were sedated with increments of midazolam (2.5 mg IV), if required. The surface landmarks for injection were as described by Moore (6). A 22 gauge, 9 cm, short bevelled spinal needle (Becton Dickinson) was inserted 3–4 cm from the midline at the level of the transverse process. Accurate needle placement was confirmed by means of image intensification. Contact was made with the transverse process and the needle tip then advanced a further 1.0–1.5 cm caudad to the transverse process to be adjacent to the vertebral foramen. No attempt was made to seek paresthesias. After a careful aspiration showed no blood, air, or CSF, a test dose of 0.5 ml bupivacaine mixed with radiographic contrast was injected to confirm loss of resistance and to exclude intravascular or intraneural needle placement. Five milliliters of solution (bupivacaine 0.75%, 3.33 ml, diluted with sodium iothalamate 70%, 1.66 ml) was slowly injected. The spread of solution was observed either with image intensification and recorded on plain AP and lateral radiographs (40 injections) or CT scanning (5 injections) after correct needle placement with the assistance of CT imaging. Radiographic patterns of spread were later confirmed by a neuroradiologist.

Table 1. Range and Site(s) of Spread of Injected Local Anesthetic Solution with Associated Sensory Blockade

Type of spread	*n* of injections*	Mean segmental sensory loss†	Mean segmental contrast spread†
Paravertebral only	8 (18)	1.43 (0–2)	2.25 (1–4)
Paravertebral and some epidural	12 (27)	2.27 (0–9)	3.92 (2–8)
Epidural and some paravertebral	5 (12)	6.6 (1–10)	9.4 (7–13)
Epidural only	14 (31)	4.66 (0–9	10.0 (5–16)
Psoas only	3 (6)	1.0 (0–2)	2.3 (2–3)
Intrapleural	3 (6)	0.3 (2–1)	6 (3–9)

*Percent in parentheses.
†Range in parentheses.

Extent of sensory blockade was determined by loss of sensation to pinprick and light touch 30 minutes after injection. Patients were asked to describe the relief of their presenting pain as good, moderate, or poor.

Measurement of Paravertebral Dimensions

The dimensions of 114 thoracic paravertebral spaces were measured in 20 consecutive patients undergoing diagnostic thoraco-abdominal CT scans. Measurements relevant to the performance of a paravertebral injection were made using the measurement program of the Siemens Somaton DH computed tomography scanner. Patients with abnormal or pathological spinal or paravertebral anatomy were excluded from this part of the study.

Results

Spread of Solution—Radiographic and Clinical Assessment

The spread of local anesthetic solution after paravertebral injection was imprecise and unpredictable. Contrast spread was not always the same in patients having repeat injections. Several different patterns of spread were seen, the types and extent of which, together with spread associated segmental sensory loss, are shown in Table 1. The patterns of spread and the frequency with which they occurred were similar after injections in the thoracic and lumbar regions. Contrast spread was confined to the paravertebral area in only 8 (18%) of the 45 injections and when this occurred sensory loss was limited to a maximum of

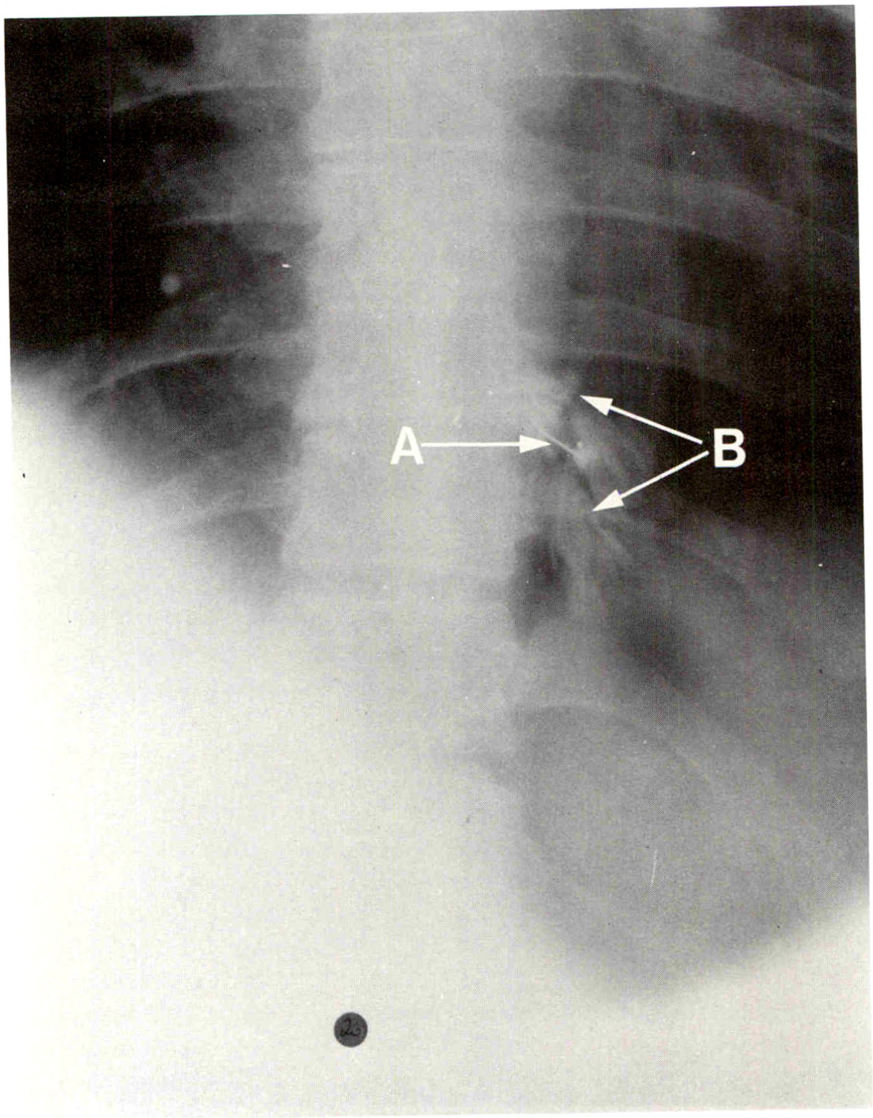

Figure 1. A plain anteroposterior radiograph that shows the needle (arrow **A**) and the injected contrast solution (arrow **B**). The solution has not spread into the epidural space in this radiograph.

two dermatomes. In only two instances was contrast observed crossing more than two rib heads but it was confined to a single segment in only one patient. Examples of spread of solution confined to the paravertebral area are shown in Figures 1 and 2.

Varying degrees of epidural spread were seen in 31 (70%) injections, and the spread was exclusively epidural after 14 (31%) (Figs. 3, 4). Combined paravertebral and epidural spread was observed in a further 17 (39%) injections (Figs. 5, 6). In the majority of these instances, the paravertebral spread remained localized to the level of injection.

Mean sensory loss was greater after epidural spread of solution when compared with paravertebral spread. However, a wide range of sensation loss was observed after both epidural and paravertebral spread (Table 1). Sensory loss, when present, was ipsilateral after all but three injections, in which bilateral sensory loss was associated with bilateral symmetrical epidural spread (Fig. 3). The mean sensory loss after these injections was seven segments (range 3–11).

Spread was solely intrapleural after three of the 34 thoracic paravertebral injections. Air was not aspirated in any of these cases and none suffered a pneumothorax. One patient coughed after injection of the solution. In all three cases the solution moved with respiration on image intensification radiography and spread to either the diaphragmatic angle or horizontal fissure of the lung. Spread was solely in to the psoas muscle in three of the 11 lumbar paravertebral injections. No paravertebral spillage was seen after these three injections. The contrast spread laterally in the direction of the muscle fibres and re-

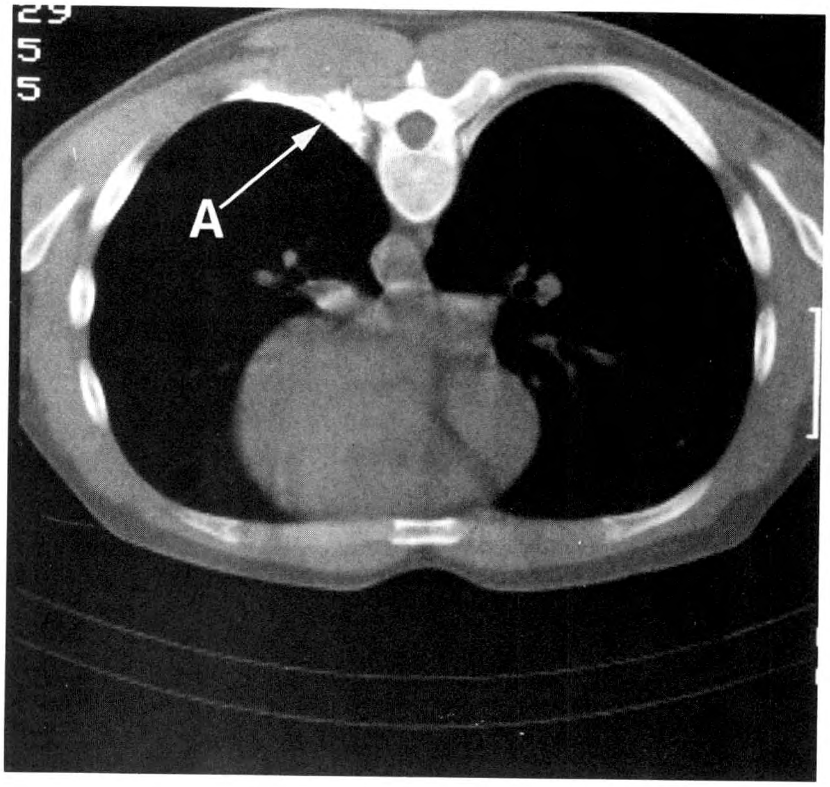

Figure 2. A computed tomography scan image that shows injected contrast solution (arrow **A**) remaining outside the vertebral canal.

sulted in a sensory loss of 0–2 segments. However all three developed motor blockade with weakness of hip flexion and knee extension.

Evidence of sympathetic blockade occurred after two injections. One patient, developed a dry vasodilated leg and another complained of bilateral nasal congestion and had a bilateral Horner's syndrome.

Relief of presenting pain was considered poor after three of the 45 blocks and moderate after five other blocks. The remainder considered pain relief to be good. In a few cases beneficial pain relief occurred in the absence of detectable sensory loss. Patients who developed sympathetic block also experienced good analgesia.

Computed Tomographic Assessment of Paravertebral Dimensions

Measurements were made from the skin surface at 3 and 4 cm from the midline to bony landmarks (transverse process and rib) and to the pleural surface and the entrance to the vertebral foramen. The results are shown in Table 2. There was a wide range in skin to transverse process (1.6–6.1 cm) and skin to rib (1.1–7.1 cm) distances, which reflects the large variations in subcutaneous fat thickness. The wide range of measurements from the transverse process to the pleura was caused by variation in the angle of the rib heads and underlying pleura with the transverse processes. The thoracic vertebral transverse process is small and the mean distance from the midline to the tip of the process was only 3.18 cm (range, 2.1–4.2 cm). This distance only exceeded 4 cm in a single measurement.

Discussion

The paravertebral space has been described as a wedge shaped space with definite anatomical boundaries. In the thoracic area the margins are formed superiorly and inferiorly by the heads and necks of the adjoining ribs and posteriorly by the superior costotransverse ligament. Anterolaterally the space is limited by the parietal pleura and the base is formed by the posterolateral aspect of the body of the vertebra and the intervertebral foramen through which it communicates with the epidural space (1,9). However, we have demonstrated spread beyond the confines of these boundaries (Figure 6) suggesting that the paravertebral space is not as anatomically discrete

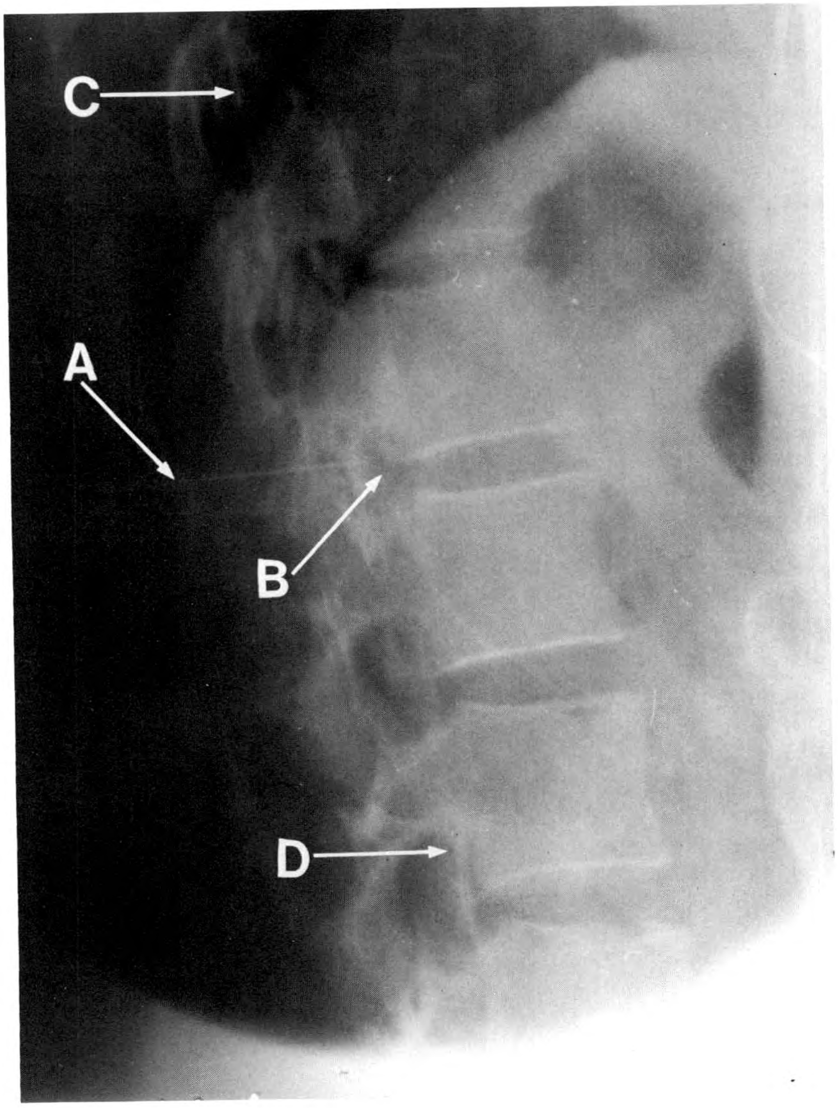

Figure 3. A plain lateral radiograph that shows the needle (arrow **A**) advanced to lie lateral to the vertebral foramen (arrow **B**). Injected contrast solution has spread up and down within the epidural space (arrows **C** and **D**).

as sometimes described. Spread of solution was restricted to the paravertebral space in only 18% of injections in this study with a maximum spread of four segments. Nevertheless, consistent spread of radiological contrast solutions in the paravertebral area, across the heads of the ribs along the vertebral bodies, has been demonstrated after intercostal (13,14) and paravertebral injections (10,11). However, these studies used injected volumes larger than those used in this study or examined the spread of dye or contrast some time after the initial injection and thus may have missed initial patterns of spread. Immediate radiological observation is necessary to determine exact spread because of rapid absorption and dissipation of contrast media in the epidural space (15) and paravertebral area (16). We observed dissipation of contrast from the epidural space within 10 minutes of injection.

Using a standardized technique we have demonstrated several types of spread. The pattern of spread was unpredictable even in the same patient receiving injections on different occasions. Therefore, the injection of radiological contrast material would seem to be essential if reliable diagnostic information is to be obtained.

Epidural spread of solution has been observed after paravertebral (17,18) as well as intercostal nerve block (14,19). The latter observation suggests that the use of a more lateral approach to the paravertebral space is unlikely to prevent spread to the epidural area. Macintosh and Mushin also proposed that ipsilateral paravertebral spread could occur only via the epidural space through communicating intervertebral foramina (17). We observed a high incidence of epidural spread (70%) associated with widespread unilateral analgesia and, in some cases, demon-

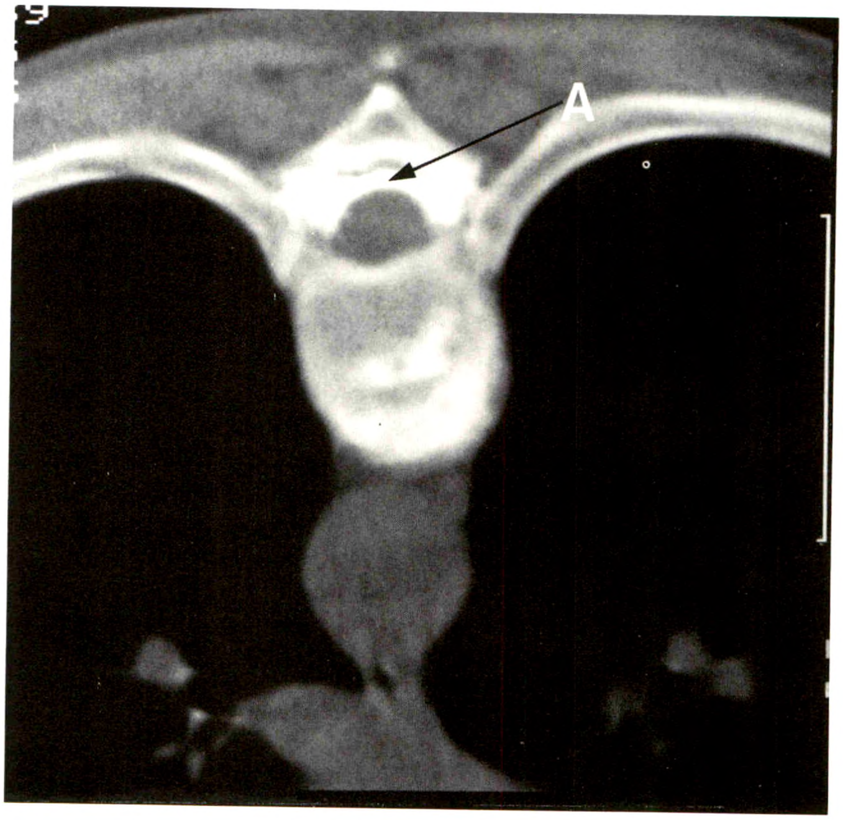

Figure 4. A computed tomography scan image that shows dense spread on injected contrast solution in the posterior epidural space (arrow **A**) after paravertebral injection.

strated spread of solution from the epidural into adjacent paravertebral spaces (Figure 5). The rapid spread of solution from the paravertebral to the epidural area may be caused by a negative pressure gradient. Indeed, when using a manometer line filled with dilute contrast to identify the point of entry into the space, we have observed solution being sucked into the epidural from the paravertebral space. The high incidence of unilateral epidural spread is consistent with the dorsal midline subdivision of the epidural space proposed by Husemeyer and White (20).

Intrapleural injection of local anesthetic solutions has recently received attention as a means of providing postoperative analgesia (21,22). Unintentional intrapleural spread occurred in three cases in this study. This would have passed unnoticed without the use of contrast medium, because air was not aspirated from the needle nor did a pneumothorax occur. The anatomical risk of a pneumothorax is reduced by entering the paravertebral space as medially as possible, pointing the needle in a median direction, because the pleura passes anteriorly at approximately 45° in the medial aspect of the paravertebral area. However, this approach increases the risk of subarachnoid injection. Nevertheless, individual variation in the distances measured by computed tomography between the transverse process and pleura was large (Table 3) and frequently fell outside the limits set by many standard texts. This suggests that the use of exact fixed distances from bony landmarks, recommended by such texts, is potentially unsafe and the consequent risk of penetrating the pleura is significant. Indeed, Cousins and Bridenbaugh have implied that the risk of pneumothorax after thoracic paravertebral injection is too great and decline to describe the procedure (23). The use of loss of resistance, upon entering the paravertebral space, to identify correct needle placement, may reduce the risk of pneumothorax, so long as the needle point is sufficiently medial, but cannot eliminate it.

It has been suggested that sympathetic blockade is not clinically significant after paravertebral block. However, we have confirmed the earlier observations of Bonica (2) who stated that sympathetic blockade was commonplace and occasionally profound after thoracic paravertebral block. The combination of sympathetic blockade and somatic blockade increases the difficulty of interpretation of the results of a diagnostic block performed to evaluate neural pathways involved in chronic pain problems.

Needle placement without radiological imaging has been shown to be inaccurate, particularly when performing lumbar and thoracic paravertebral somatic nerve blocks (24). Injection at the wrong nerve

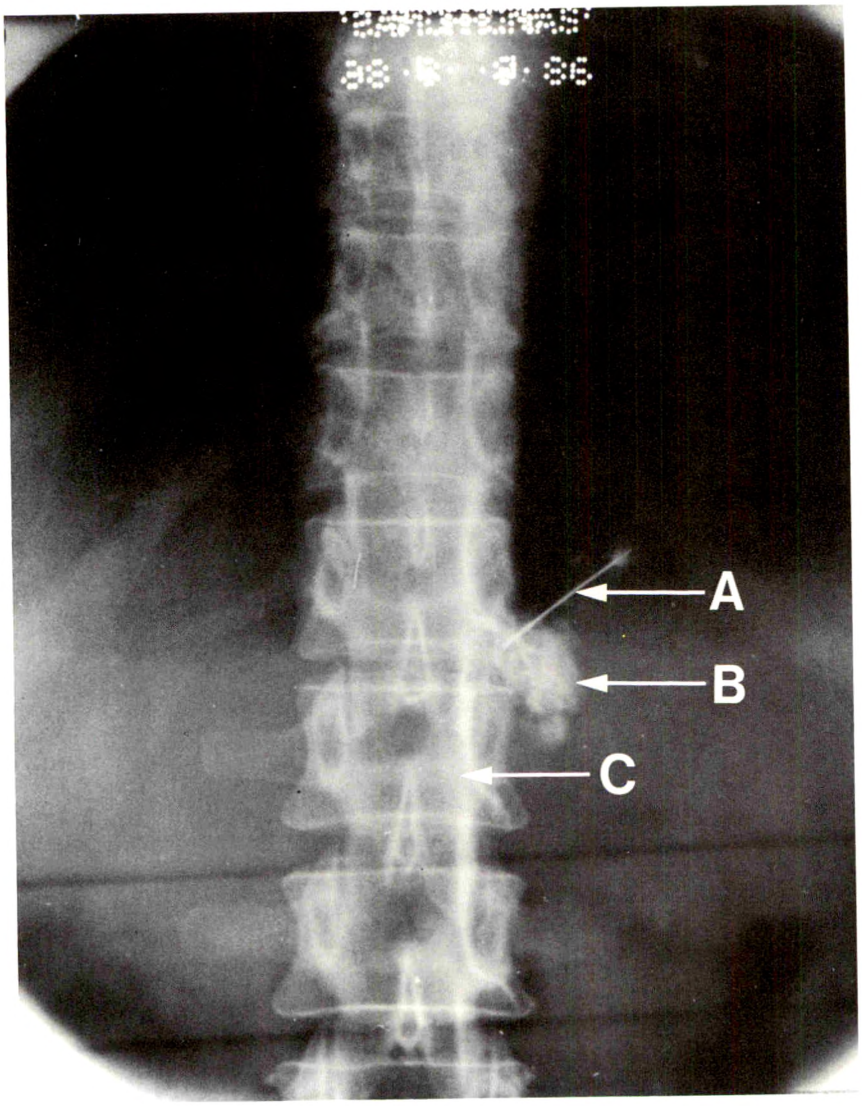

Figure 5. A plain anteroposterior radiograph that shows the needle (arrow **A**) and the injected contrast solution in the paravertebral space (arrow **B**) and within the epidural space (arrow **C**).

root and misidentification of the transverse process are the commonest faults. A potential source of error is the narrow width of the thoracic transverse process noted on CT measurement. (mean, 3.18 cm; range, 2.1–4.2 cm). Consequently, an unwary operator may, without radiological imaging, easily miss the transverse process and either mistake the first contact with rib for transverse process or worse, penetrate the pleura.

In conclusion, it was not the intention of this study to demonstrate the superiority of any particular technique but to illustrate what may happen to a solution when injected from a needle tip positioned in the paravertebral space. Such a position may be arrived at by a number of advocated techniques. The findings of this study indicate that the spread of solution after paravertebral injection is unpredictable and may be extensive, despite the use of small volumes. Solution spread confined to a single nerve root was exceptional. Variations in technique cannot guarantee that a solution is not spreading in the diverse ways that we have demonstrated unless contrast medium is also injected. Consequently, diagnostic paravertebral injections must be interpreted with extreme caution. It would be difficult to justify neuroablative procedures (e.g., rhizotomy or chemical neurolysis) on the basis of a diagnostic paravertebral injection alone. Furthermore, the injection of neurolytic solutions into the paravertebral space without the use of radiological contrast must be regarded as hazardous.

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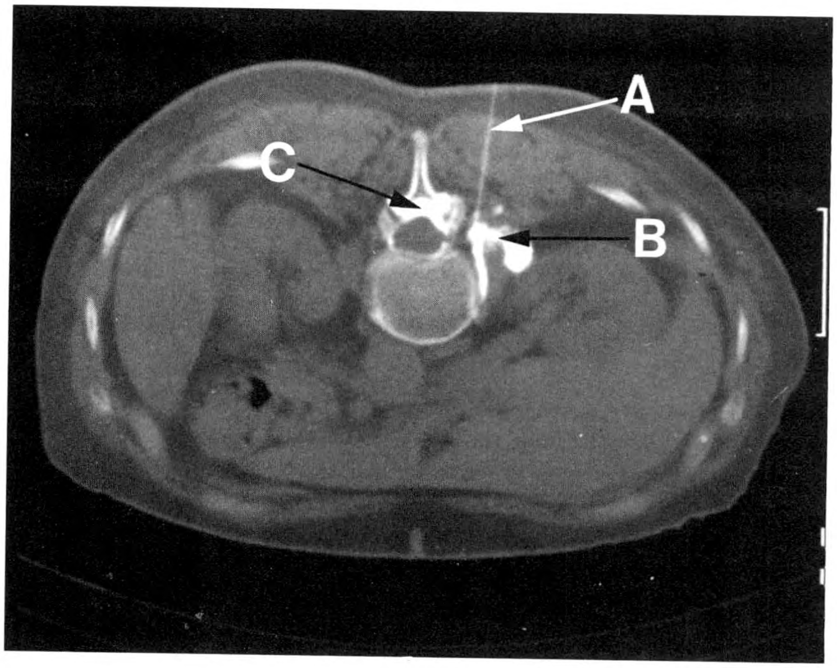

Figure 6. A computed tomography scan image that shows the needle (arrow **A**) and injected contrast solution in the paravertebral space (arrow **B**) and within the epidural space (arrow **C**).

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ANESTH ANALG
1989;68:40–5

Plasma Atrial Natriuretic Polypeptide and Angiotensin II in Rats during Anesthesia and Volume Loading

William E. Hoffman, PhD, M. Ian Phillips, PhD, and Birgitta Kimura, BA

HOFFMAN WE, PHILLIPS MI, KIMURA B. Plasma atrial natriuretic polypeptide and angiotensin II in rats during anesthesia and volume loading. Anesth Analg 1989;68:40–5.

These experiments investigated the effect of halothane or fentanyl anesthesia on plasma atrial natriuretic polypeptide (ANP) and angiotensin II (AII) concentrations and the response to a 30% blood volume load in rats. Halothane (1.1% and 2.2% inspired) or fentanyl (50 and 200 μg/kg) anesthesia alone produced little change in basal plasma ANP levels but did increase plasma AII levels above unanesthetized baseline concentrations. A 30% blood volume load in conscious rats produced a transient increase in blood pressure and central venous pressure, a threefold rise in plasma ANP, and a decrease in AII. These effects were not significantly altered by fentanyl anesthesia. In contrast, during 2.2% halothane anesthesia the increase in plasma ANP produced by volume loading was greater and the decrease in AII was abolished. These results indicate that fentanyl does not increase basal ANP levels or markedly change the hormonal response to a volume load. Altered responses seen during deep halothane anesthesia may result from cardiovascular changes or a direct stimulation of physiological mechanisms that release ANP.

Key Words: ANESTHETICS—volatile, halothane. ANESTHETICS—intravenous, fentanyl. POLYPEPTIDES—atrial natriuretic, angiotensin II.

Angiotensin II (AII) and atrial natriuretic polypeptide (ANP) appear to have opposite effects in several physiological functions. Angiotensin II is released by hypovolemic stimuli whereas ANP is released by acute hypertension and hypervolemia and is directly related to stimulation of right atrial receptors (1–3). In addition, many of the cardiovascular and renal effects of AII and ANP are opposite. Atrial natriuretic polypeptide produces natriuresis and vasodilation and inhibits renin secretion and AII-induced aldosterone release in intact animals (4,5). The effects of anesthetics on plasma ANP have not been studied systematically. Preliminary studies concerning the effects of anesthetics on ANP release indicate that morphine and halothane increase plasma ANP concentration and that halothane blocks ANP release produced by volume expansion (6,7). These studies suggest that both opiates and halothane stimulate ANP release and alter receptor-mediated release. However, the level of anesthesia was not reported in these studies and arterial blood gas tensions and other physiological variables were apparently not controlled. These factors may have had an impact on the results reported. Here we have investigated the effects of halothane and fentanyl on plasma AII and ANP concentrations measured by radioimmunoassay and the effect of those anesthetics on the response to a hypervolemic challenge.

Methods

Male Sprague–Dawley rats (400–500 g) were maintained on a 12 hour light–dark cycle with food and water supplied ad libitum. This study received prior IRB approval for animal research. In the first experiment, rats were tested on separate days under unanesthetized conditions, during halothane anesthesia or during fentanyl anesthesia. On day one, seven rats were anesthetized with halothane, and saline filled catheters were inserted in the femoral artery and jugular vein and tunneled under the skin to exit at the back of the neck. Each rat was allowed one day to recover from the surgical and anesthetic effects. On day two, arterial blood pressure and heart rate were

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Address correspondence to Dr. Hoffman, Department of Anesthesiology, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, IL 60616.

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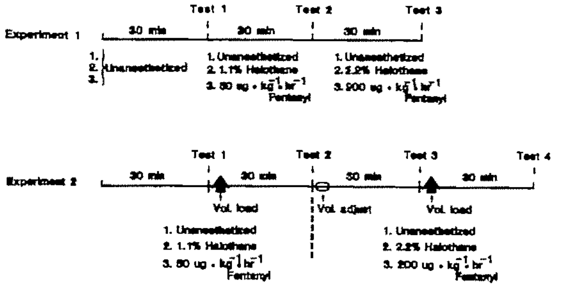

Figure 1. Protocol for experiments 1 and 2. The numbers under the time line for each experiment represent the treatment groups (e.g., 1, 2, and 3) and treatment conditions. Arrows above the time line indicate the time of blood sampling. In experiment 2 a 30% blood volume increase or volume regulation was made immediately after blood samples were taken.

measured for 15 minutes and a 2-ml blood sample was drawn for baseline measurement of arterial blood gas tensions, and plasma levels of AII and ANP (Fig. 1). The blood (2 ml) was added to an inhibitor combination containing 2 nmol leupeptin, 3 nmol pepstatin A, 54 KIU aprotinin, 0.5 μmoles PMSF, and 3 μmoles EDTA per milliliter of blood. Samples were centrifuged, the plasma eluted and frozen at −80°C. The withdrawn blood was replaced with donor rat blood. The above measures and blood samples were repeated 30 minutes (sample 2) and 1 hour later (sample 3). On day 3, hemodynamic measurements were made and blood samples taken from the same rats during halothane anesthesia. The first sample was obtained under baseline unanesthetized conditions. The second sample was taken 30 minutes after tracheal intubation and pulmonary ventilation with 1.1% inspired halothane in oxygen. $Paco_2$ was maintained between 35 and 40 mm Hg during all test conditions and rectal temperature at 37°C. The third sample was obtained 30 minutes after the start of ventilation with 2.2% inspired halothane. Blood was replaced with donor blood as before. On day 4 the effects of fentanyl anesthesia were tested in the same rats. The first sample was taken during baseline unanesthetized conditions. The second sample was taken 30 minutes after tracheal intubation, paralysis with 1 mg/kg *d*-tubocurarine, injection of a 25 μg/kg bolus of fentanyl and infusion of fentanyl at a rate of 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The third sample was obtained following a 30 minute infusion of 200 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ fentanyl. Withdrawn blood was replaced with donor blood as in previous days.

In experiment 2, separate groups of rats were tested unanesthetized (group 1, $n = 6$) and during halothane (group 2, $n = 6$) or fentanyl anesthesia (group 3, $n = 6$). Unanesthetized rats in group 1 were prepared with chronically implanted femoral artery and jugular vein catheters under halothane anesthesia one day before testing as described above. The jugular catheter was advanced 3 cm to allow measurement of central venous pressure (CVP). On day 2, arterial blood pressure, central venous pressure (CVP), arterial blood gas tensions and a 2-ml blood sample for AII and ANP measurement were taken under four test conditions (Fig. 1). The first was an unanesthetized baseline measurement. The second sample was taken 30 minutes after a 30% blood volume transfusion from a donor rat, with blood volume calculated as 6% of body weight. The third sample was taken 30 minutes after blood volume was readjusted to baseline levels by withdrawing blood. The fourth sample was taken 30 minutes after a second 30% blood volume load. All blood samples were prepared as described in experiment one.

Rats tested during halothane were anesthetized in a bell jar with halothane. After tracheotomy the lungs were ventilated with 1.5% halothane and femoral artery and jugular vein catheters inserted. The inspired halothane concentration was then adjusted to 1.1% in oxygen and the rat allowed to equilibrate for 30 minute. The first sample was then taken. The second sample was taken 30 minutes after a 30% blood volume transfusion. The blood volume was then adjusted to baseline levels and the halothane concentration changed to 2.2% inspired. After an additional 30 minutes a third sample was obtained from each rat. The fourth sample was then made 30 minutes after a 30% blood volume transfusion.

Rats tested during fentanyl were initially anesthetized and surgically prepared using halothane anesthesia. They were then paralyzed with 1 mg/kg *d*-tubocurarine the halothane withdrawn and the rats given a 25 μg/kg fentanyl bolus followed by an infusion of 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ fentanyl for 30 minutes. The first sample was then taken. The second sample was collected 30 minutes after a 30% blood volume load with the same fentanyl infusion rate. The blood volume was adjusted to control levels and a third sample taken 30 minutes after the start of a fentanyl infusion of 200 $\mu g \cdot kg^{-1} \cdot hr^{-1}$. The fourth sample was obtained 30 minutes after a 30% blood volume load during the infusion of 200 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ fentanyl. Rats were killed at the end of each experiment with an overdose of anesthesia.

ANP and AII Assays

ANP was purified from plasma samples using Sep-Pak C18 cartridges (Octadecyl Silica, Waters Assoc). Plasma samples were acidified using 1% trifluoroace-

Table 1. Cardiovascular and Blood Gas Changes during Halothane and Fentanyl Anesthesia

Group	*n*	Treatment	Blood pressure (mm Hg)	Heart rate (beats/min)	Paco_2 (mm Hg)	Pao_2 (mm Hg)	Arterial pH
Unanesthetized	7	Baseline	107 ± 2	345 ± 11	38.3 ± 1.2	95 ± 4	7.45 ± 0.01
		Sham	104 ± 3	348 ± 7	36.0 ± 1.1	96 ± 4	7.47 ± 0.01
		Sham	103 ± 2	353 ± 8	34.8 ± 1.1	93 ± 1	7.45 ± 0.01
Halothane	7	Baseline	98 ± 3	338 ± 13	35.2 ± 1.0	94 ± 2	7.47 ± 0.01
		1.1%	92 ± 5	336 ± 8	35.7 ± 1.0	359 ± 45*	7.45 ± 0.01
		2.2%	57 ± 3*	280 ± 5	36.2 ± 0.9	352 ± 30*	7.42 ± 0.01
Fentanyl†	7	Baseline	98 ± 3	348 ± 19	37.1 ± 1.1	88 ± 2	7.47 ± 0.01
		50 μg	123 ± 4*	379 ± 19	35.9 ± 0.6	391 ± 26*	7.44 ± 0.01
		200 μg	130 ± 5*	396 ± 47	36.7 ± 1.6	362 ± 40*	7.38 ± 0.02*

*$P < 0.05$ anesthesia vs control.
†Fentanyl doses represent $\mu g \cdot kg^{-1} \cdot hr^{-1}$ infusion rate.

tic acid (TFA) and added to the Sep-Pak columns. ANP was eluted from the columns using a methyl alcohol–water–TFA solution (80:19:1) and concentrated by air drying the eluate at 30°C. The recovery of ANP using these procedures was 85%. A double antibody method was used for the ANP radioimmunoassay. Atrial natriuretic peptide (rat 28 amino acids) and rabbit ANP antibody were obtained from Peninsula Laboratories and goat anti-rabbit IgG antibody from Biotek Research Inc. The ANP antibody crossreacts 100% with alpha-human ANP, ANP (8–33) and atriopeptin III. It crossreacts 60% with ANP (18–28), 10% with auriculin A, and 5% with atriopeptin II. There is no cross reactivity with atriopeption I or unrelated peptides such as vasopressin, oxytocin and somatostatin. The ED_{50} is 23 pg. The intra- and interassay coefficients of variation are 4.5% and 13.5% respectively.

Angiotension II was purified from plasma using an acidic acetone extraction. The radioimmunoassay for AII is the method of Phillips and Stenstrom (8) using rabbit anti-angiotensin II antibody (Ab2). Dextran-coated charcoal was used for separation of antibody bound and free angiotensin in the assay. It crossreacts 100% with angiotension III, but 0.5% with angiotensin I and has no crossreactivity with vasopressin, substance P or bradykinin. The Ed_{50} is 9 pg and the intra- and interassay coefficients of variation are 8.4% and 15.8% respectively.

Results are expressed as means ± SEM. Statistical differences were analyzed with repeated measures of analyses of variance and Scheff's test for multiple testing of individual group means. A value of $P < 0.05$ was considered statistically significant.

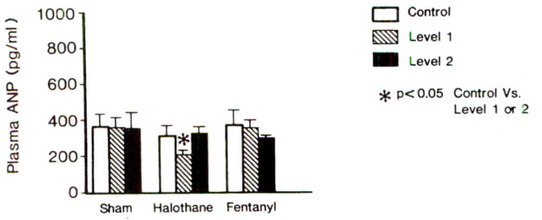

Figure 2. Plasma ANP levels during halothane and fentanyl anesthesia. Baseline values are unanesthetized. Sham treated rats were unanesthetized for all three treatments. Halothane levels 1 and 2 are 1.1% and 2.2% inspired concentrations, respectively. Levels 1 and 2 for fentanyl are 50 and 200 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, respectively. Number of rats = 7 for all tests, as shown in Table 1.

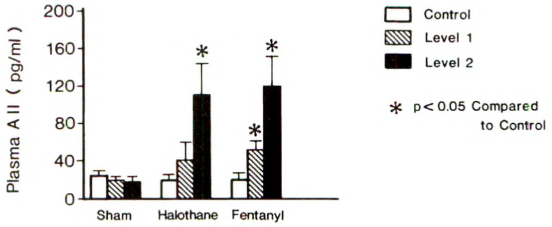

Figure 3. Plasma AII changes during halothane and fentanyl. Treatments are as described in Figure 1.

Results

Blood pressure and arterial blood gas tensions under unanesthetized conditions and during halothane and fentanyl anesthesia are shown in Table 1. Pao_2 increased during anesthesia because of use of 100% oxygen in the ventilating gases, but pH remained at baseline levels. Unanesthetized rats showed no significant changes in blood pressure during the test period. Halothane 2.2% decreased blood pressure, whereas 50 μg and 200 μg fentanyl doses produced an increase in blood pressure. Plasma ANP and AII during halothane and fentanyl anesthesia are shown in Figures 2 and 3. Neither ANP nor AII concentrations changed with repeated samples in unanesthetized rats. Halothane produced a small but statistically significant decrease in ANP at the lowest dose (1.1% inspired), but 2.2% halothane did not produce

Table 2. Cardiovascular and Blood Gas Changes during Anesthesia and Volume Loading

Group	*n*	Treatment	Blood pressure (mm Hg)	Heart rate (beats/min)	Central venous pressure (mm Hg)	Paco$_2$ (mm Hg)	Pao$_2$ (mm Hg)	Arterial pH
Unanesthetized	6	Baseline	115 ± 2	360 ± 15	2 ± 1	35.9 ± 1.1	101 ± 6	7.44 ± 0.01
		30% load	116 ± 5	333 ± 10	4 ± 1*	35.7 ± 0.7	95 ± 7	7.44 ± 0.01
		Baseline	107 ± 4	373 ± 7	2 ± 1	35.0 ± 0.5	97 ± 6	7.45 ± 0.01
		30% load	114 ± 4	350 ± 7	4 ± 1*	35.2 ± 0.8	93 ± 3	7.45 ± 0.01
Halothane	6	1 MAC	88 ± 8	283 ± 12	2 ± 1	37.1 ± 1.1	411 ± 11	7.43 ± 0.01
		30% load	112 ± 4*	305 ± 7	2 ± 1	40.3 ± 1.0	372 ± 22	7.42 ± 0.01
		2 MAC	65 ± 8	273 ± 11	3 ± 1	37.6 ± 1.0	359 ± 32	7.41 ± 0.01
		30% load	78 ± 4*	293 ± 10	5 ± 1*	38.9 ± 1.7	304 ± 29	7.41 ± 0.01
Fentanyl†		50 μg	135 ± 5	340 ± 20	4 ± 1	38.5 ± 2.1	308 ± 67	7.41 ± 0.01
		30% load	151 ± 3*	366 ± 22	5 ± 1	39.0 ± 0.8	267 ± 60	7.41 ± 0.01
		200 μg	136 ± 4	373 ± 39	3 ± 1	35.2 ± 1.0	344 ± 55	7.41 ± 0.01
		30% load	157 ± 3*	416 ± 20	6 ± 2*	38.5 ± 1.5	309 ± 51	7.42 ± 0.01

*$P < 0.05$ volume load vs group anesthetized control before volume loading.
†Fentanyl dose represent μg·kg^{-1}·hr^{-1}.

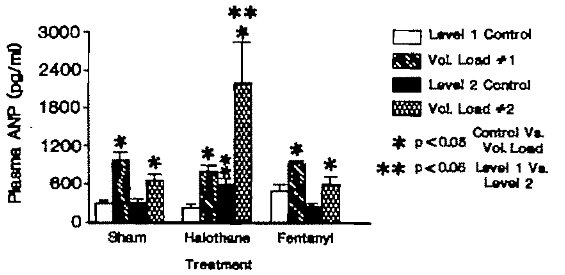

Figure 4. Plasma ANP during halothane or fentanyl and a 30% volume load. Sham treated rats were unanesthetized for tests. Halothane levels 1 and 2 are 1.1% and 2.2% inspired concentrations, respectively. Levels 1 and 2 for fentanyl are 50 and 200 μg·kg^{-1}·hr^{-1}, respectively.

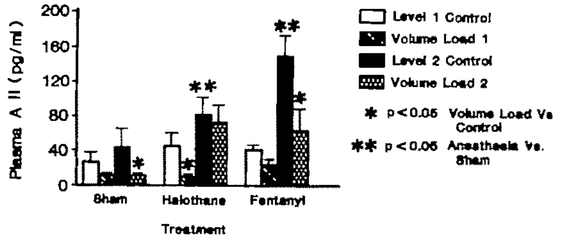

Figure 5. Plasma AII during halothane or fentanyl and a 30% volume load. Treatments are as described in Figure 4.

a change in ANP compared to control values (Fig. 2). Neither the low nor the high dose of fentanyl changed plasma ANP concentration. Both halothane and fentanyl anesthesia resulted in dose related increases in AII which were significant with 2.2% halothane and 50 and 200 μg fentanyl (Fig. 3).

Table 2 summarizes changes in blood pressure and arterial blood gas tensions during anesthesia and volume loading. A 30% blood volume load given to unanesthetized rats resulted in a transient 23 ± 5 mm Hg increase in blood pressure and a 4 ± 1 mm Hg increase in CVP. Thirty minutes after the volume load both parameters had returned close to baseline levels. Volume loading produced a threefold increase in plasma ANP in unanesthetized rats (Fig. 4). This increase was still apparent but was attenuated after a second volume load in unanesthetized rats. Plasma AII decreased in unanesthetized rats after a 30% volume load (Fig. 5).

Volume loading in halothane-anesthetized rats produced immediate increases in blood pressure (1.1% halothane = 26 ± 5 mm Hg; 2.2% halothane = 31 ± 8 mm Hg) and CVP (1.1% halothane = 3 ± 1 mm Hg; 2.2% halothane = 5 ± 1 mm Hg) that did not return to baseline levels during the 30-minute equilibration period. Atrial natriuretic polypeptide increased with volume loading during 1.1% halothane anesthesia in a manner similar to that seen in unanesthetized rats (Fig. 4). During 2.2% halothane the increase in ANP concentration in response to volume loading was significantly greater compared to unanesthetized animals. Angiotensin II decreased significantly after volume loading during 1.1% but not during 2.2% halothane (Fig. 5).

Volume loading during fentanyl anesthesia produced immediate increases in blood pressure (50 μg = 23 ± 5 mm Hg; 200 μg = 27 ± 2 mm Hg) and CVP (50 μg = 3 ± 1 mm Hg; 200 μg = 3 ± 1 mm Hg) both of which remained elevated 30 minutes later. Volume loading increased ANP and decreased AII concentrations with both doses of fentanyl. These relative changes were similar to those seen in unanesthetized rats (Figs. 4 and 5).

Discussion

These results show that halothane and fentanyl anesthesia produce little change in plasma ANP but that both anesthetics increase plasma AII. In unanesthetized control rats, a 30% blood volume load produced an increase in plasma ANP and a decrease in plasma AII. These responses were not altered by low or high dose fentanyl anesthesia or by 1.1% inspired halothane. In contrast, during 2.2% halothane the increase in plasma ANP was greater after a volume load and the decrease in plasma AII was abolished. This suggests that deep halothane anesthesia may alter normal mechanisms that control ANP and AII release by changing the cardiovascular response to a volume load or by a direct drug action at the volume receptor or the central nervous system.

There is little information concerning the effect of opiate stimulation on ANP and AII concentrations. Gutkowska et al. (6) reported that 100 mg/kg morphine produced a 25-fold increase in plasma ANP. The relevance of this report is questionable, however, because smaller doses were not tested and blood pressure and blood gas tensions were not controlled or reported. Our data indicate that fentanyl increases blood pressure but does not increase plasma ANP or alter the release produced by volume loading. In contrast, 200 μg/kg fentanyl significantly increased plasma AII. This is consistent with a report by Bailey et al. (9) that 1–3 mg/kg morphine produced a 3.5-fold increase in renin activity in man. These results show that fentanyl produces an increase in plasma AII in the rat but does not change the decrease in AII produced by volume loading.

As with opiate anesthesia, there is little information concerning the effect of halothane on plasma ANP. Eskay et al. (7) reported that halothane produced a 2.5-fold increase in plasma ANP compared to unanesthetized controls and inhibited the increase in ANP produced by volume loading. However, there was no indication of the halothane concentration used. Blood gas tensions and body temperature also were not reported and apparently not maintained constant during the study. This makes their results difficult to interpret. Our results show that 2.2% inspired halothane, equivalent to 2 MAC in the rat (10), does not increase plasma ANP but produces a greater increase in plasma ANP to volume loading. This greater response may be related to the transient increase in blood pressure and CVP produced by volume loading in 2.2% halothane anesthetized rats, which was higher than in unanesthetized controls. Other possible mechanisms include a nonlinear response of right atrial receptors to changes in volume or a direct action of halothane at the receptor or central nervous system to increase ANP release.

With respect to the renin–angiotension system, Pettinger et al. (11) reported that in rats, 2% halothane produces a modest twofold increase in renin activity. Miller et al. (12) found no increase in renin activity during 1 MAC halothane, but significant hypotensive effects seen during infusion of an AII antagonist suggested that plasma AII was elevated. Our data indicate that 2.2% inspired halothane increases plasma AII concentration and inhibits the decrease in AII normally seen after volume loading. Both of these effects may be related to the hypotension and baroreceptor stimulation produced by deep halothane anesthesia.

There are several methodological problems that need to be considered in this study. The first is the use of donor rat blood for volume loading and to allow multiple blood samples in the same rat. Replacement blood from an untreated donor would not contain the same anesthetic or hormonal concentrations as the experimental animal. An attempt was made to control this by using unanesthetized rats as a sham group and showing that donor blood replacement did not change ANP or AII values in repeated measures. A 30-minute interval was considered to be an adequate period for ANP and AII to equilibrate with endogenous blood because of the short half-life of both hormones (13,14).

A second problem is equating different states of halothane and fentanyl anesthesia in the rat. It has been shown that 1.1% inspired halothane approximates 1 MAC anesthesia in the rat (10) and produces a 30% depression in cerebral metabolic rate (15). Two MAC halothane will produce a slightly greater depression of brain metabolism, but higher levels than this will produce toxic effects (16). Shingu et al. (17) measured MAC equivalent for fentanyl in rats and reported an ED_{50} or MAC level of 52 μg/kg for subcutaneous injections. Other researchers have shown that 50 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ fentanyl produces a cerebral metabolic depression of 30% whereas 200 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ produces a maximum 40% depression (18). Therefore, the anesthetic doses of halothane and fentanyl chosen may represent approximately equivalent anesthetic states for testing.

In conclusion, these results have shown that anesthetic levels of halothane and fentanyl produce little change in plasma ANP but increase plasma AII. The results regarding AII release are consistent with previous reports (10,11), but we did not observe the marked increase in plasma ANP that has been seen previously with opiate drugs and halothane (6,7). Our data suggest that fentanyl does not stimulate

ANP release and does not significantly alter the normal change in plasma ANP or AII to volume loading. Halothane (2.2% inspired) increases the response of plasma ANP to a volume load while antagonizing an expected decrease in plasma AII. The changes may reflect altered cardiovascular responses to a 30% volume load during deep halothane anesthesia or a direct stimulation by halothane of neural mechanisms that release ANP.

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Chronically Administered Progesterone Decreases Halothane Requirements in Rabbits

S. Datta, MD, R. P. Migliozzi, BA, H. L. Flanagan, MD, and N. R. Krieger, PhD

DATTA S, MIGLIOZZI RP, FLANAGAN HL, KRIEGER NR. Chronically administered progesterone decreases halothane requirements in rabbits. Anesth Analg 1989;68:46–50.

The MAC for halothane is 25% lower in pregnant than that in nonpregnant ewes. The reason for this is uncertain, but changes in both steroidal and endogenous opiate have been implicated. This study was undertaken to assess the effect of exogenous progesterone on minimal alveolar concentrations (MAC) of halothane in ovariectomized rabbits. Minimal alveolar concentration of halothane was determined in 84 female rabbits, 37 intact (group A), 20 ovariectomized and injected with inert carrier peanut oil (group B), and 27 ovariectomized and injected with progesterone in peanut oil (group C). Minimal alveolar concentration in group A, 1.68 ± 0.06% (mean ± SEM), did not differ significantly from that in group B rabbits, 1.77 ± 0.06%. However, MAC in progesterone-treated rabbits, 1.48 ± 0.06%, was significantly lower than the MAC of the other two groups ($P < 0.01$). Plasma progesterone concentrations in group A, B, and C were 5.28 ± 0.62 ng/ml, 6.83 ± 2.00 ng/ml, and 37.33 ± 4.25 ng/ml, respectively. These results suggest that experimental treatment with progesterone can reduce the amount of halothane required to produce anesthesia and may explain the phenomenon of decreased need of inhalation anesthetic in human parturients.

Key Words: ANESTHETICS, VOLATILE—halothane. POTENCY, ANESTHETIC—MAC. PREGNANCY—HALOTHANE—MAC. ANESTHESIA, obstetric.

Pregnancy is associated with reduction in the amount of anesthetic required to produce general anesthesia with inhalational agents or regional anesthesia with local anesthetics. The minimal anesthetic concentration (MAC) for halothane in ewes is 25% less than it is in nonpregnant controls (1). Women at term need 25% less local anesthetic for epidural anesthesia than do nonpregnant women (2). Action potentials in excised vagus nerves from pregnant rabbits are more sensitive to anesthetic effects of bupivacaine than are nerves from nonpregnant rabbits (3,4). The explanation for these observations is not clear and may differ with local and inhalation anesthetics. The high progestin and opiate levels characteristics of pregnancy may be involved. In previous studies, we compared plasma endorphin and progesterone concentrations in nonpregnant women and parturients (5,6). Plasma opiate levels were not significantly different but progesterone levels differed by 60-fold.

Palahniuk et al. (1) and Merryman et al. (7) suggest that progesterone may be responsible for changes in inhalation anesthetic requirements during pregnancy. The regulation of behavior by the actions of steroids on nervous tissue is well documented (8–10). Modulation of CNS activity by endogenous steroids could explain the decreases in MAC observed during pregnancy, and administered steroids could decrease MAC for inhalation anesthetics like halothane. Here we have tested these possibilities by comparing MAC for halothane in ovariectomized rabbits injected with progesterone with control animals either intact or ovariectomized and injected with vehicle only. MAC values in rabbits injected with progesterone were significantly lower.

Materials and Methods

Eighty-four New Zealand female white rabbits (supplied by Milbrook Farm of New England) (weight, 4.5–5.5 kg) were studied. Animals were housed in the Harvard Medical School NIH-approved animal care

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Address correspondence to Dr. S. Datta, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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facility in accordance with the "Guide for the care and use of laboratory animals" (DHHS publication no. [NIH] 78-23 revised 1978) and treated in accordance with the Harvard Medical Area criteria. Rabbits were classified into three groups. Group A ($n = 37$) consisted of intact animals, groups B ($n = 20$) and C ($n = 27$) were made up of ovariectomized rabbits injected with peanut oil alone and with progesterone in peanut oil, respectively. After bilateral ovariectomies, 14 days were allowed for recovery. Animals were then given injections over an 8-day period. MAC was determined on the ninth day. Progesterone in peanut oil (2 ml) or peanut oil alone was injected IM (10 mg/kg per day) on four successive afternoons, Monday through Thursday, with a bolus dose of 30 mg/kg (6 ml of peanut oil) on Friday afternoon, and a final dose 10 mg/kg (2 ml of peanut oil) on the following Monday afternoon. Treatment was for 8 days because Goto and Csapo (11) observed a maximum increase in membrane potential of the myometrium after treating guinea pigs with ovarian steroids for 5–10 days. Females were used because the hypothesis tested has to do with anesthesia of parturients; ovariectomy was intended to eliminate any background contribution of the ovary to progesterone levels. The progesterone powder (Sigma Chemical Co., St. Louis, MO) used was dissolved in 2–4 ml of absolute ethanol and 16 ml of peanut oil. The solution was stored at 4°C after stirring to allow the alcohol to evaporate. The rabbits were injected (24°C) in different areas of the paravertebral muscles.

MAC was determined as described by Drummond (12) with modifications. Induction of anesthesia was accomplished with halothane and oxygen and the trachea was intubated with a number 3.5 portex tube. The animals were ventilated mechanically (tidal volume 15 ml/kg; rate, 20 breaths/min approximately). Esophageal temperature was controlled at 40°C using a warming pad. Expired halothane and carbon dioxide concentrations were monitored continuously using an Engström Emma and a capnometer (Hewlett-Packard 4721081). Emma measures inspired and end-tidal gas concentrations breath by breath with a quartz crystal transducer. Anesthesia was initially maintained with 2% halothane for 60 minutes to approximate steady-state concentrations in alveolar gas (end-tidal), arterial blood and the brain as measured by the Emma. After ventilation with 1.4% halothane (a concentration selected on the basis of a pilot study) for 20 minutes, the rabbits were stimulated by clamping proximal one-third of the shaved tail with a rubber shod hemostat (Carmalt hemostatic forceps 6 ¼") closed to first ratchet. The hemostat was continuously moved 60 seconds and then removed. Any purposeful movement by the rabbit constituted a positive response. Stiffening, shivering, swallowing, or changes in respiratory pattern were not considered purposeful. The end-tidal concentration halothane was then adjusted by 20% of the existing value (upward after a positive response, downward after a negative) and maintained for 20 minutes at the new end-tidal concentration before again clamping the tail. When the "no response" concentration was obtained in this fashion, the intermediate end-tidal halothane concentration (i.e., a 10% adjustment) was used and, after 20 minutes, a final clamping was performed. MAC was defined as the mid-point between the lowest end-tidal concentration at which a negative response occurred and the highest concentration at which a positive response was observed. The MAC value thus obtained allowed a maximum error of ±5%. MAC for each group of animals was calculated as the mean of all the animals in that group. All studies were performed by afternoon after allowing at libitum access to food and water until time of study.

Three to four milliliters of blood were drawn from the rabbits (from the ear vein) on the day of MAC determination. Plasma progesterone concentrations were determined by radioimmunoassay with antiserum raised from rabbits. The lower limit of sensitivity was 10 to 25 pg of progesterone (13). Tritiated (^3H) progesterone was obtained from New England Nuclear (Du Pont NEN Research product; Boston, MA).

The statistical significance of the results was examined by means of an analysis of variance, with groups (A versus B versus C) as the single factor. The overall results were then decomposed into two planned orthogonal contrasts which compared 1) the mean MAC value of group A with that of group B, and 2) the mean MAC value of group C with the average of the mean values exhibited by groups A and B. The degree of correlation of progesterone concentration and MAC was evaluated using linear regression analysis. Plasma progesterone levels were measured in 27, 20, and 25 animals of groups A, B, and C, respectively. The number of progesterone measurements in the three groups was less than the number of measurements of MAC because blood levels were not determined for every animal. The criterion for statistical significance was $P < 0.05$.

Results

Figure 1 shows the MAC for halothane in intact rabbits (group A), ovariectomized rabbits treated with peanut oil (group B), and ovariectomized rabbits

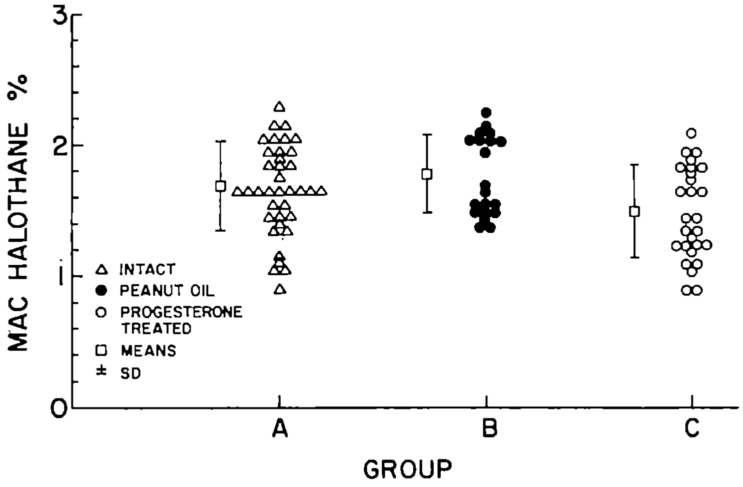

Figure 1. Halothane MAC in three groups of rabbits (mean ± SD). Group A (Δ), intact; group B (●), (ovariectomized) and injected with peanut oil; group C (○), ovariectomized and injected with progesterone in peanut oil.

treated with progesterone (group C). MAC values in control animals (group A and group B) and progesterone-treated animals (group C) were 1.68 ± 0.06%; 1.77 ± 0.06%, and 1.48 ± 0.06%, respectively. The analysis of variance revealed an overall group effect ($F = 4.694$, D.F. = 2/81, $P = 0.012$). Two planned orthogonal contrasts indicated that: 1) There was no significant difference between the MAC values of groups A and B, the two control groups (T = 1.00, D.F. = 81, $P > 0.15$); 2) Group C exhibited a significantly lower MAC value than the average of the mean MAC values from groups A and B (T = 3.02, D.F. = 81, $P < 0.01$). Although the means of MAC in intact (group A) and in vehicle-injected (group B) ovariectomized animals are similar, the distribution of MAC values in these two groups of rabbits (Fig. 1) appear to differ. In the vehicle-treated groups there are no MAC values below 1.4%. In contrast, the group that received progesterone has a distribution similar to that for the intact animals (MAC values do occur below 1.4%). Tidal volume, respiratory rate, and end-tidal CO_2 tension were not different in the experimental and control groups.

Plasma progesterone concentrations in groups A, B, and C were 5.28 ± 0.62 ng/ml, 6.83 ± 2.00 ng/ml, and 37.33 ± 4.25 ng/ml, respectively. In progesterone-treated animals (group C), MAC and plasma progesterone concentrations in the interval between 10 ng/ml and 50 ng/ml are closely fitted by a straight line ($r = 0.53$; $P < 0.05$) as seen in Figure 2. Four of the higher progesterone concentrations shown in Figure 2 are not included in this fit. Alternatively, functions can be drawn through all the points but such functions have the disadvantage of being double valued. Correlations between plasma progesterone concentrations and MAC in groups A or B were not apparent.

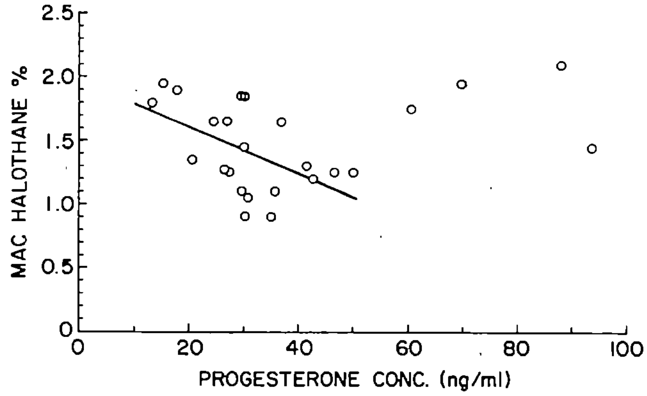

Figure 2. MAC values vs plasma progesterone concentrations for ovariectomized animals injected with progesterone (group C). The plasma concentrations from 10–50 ng/ml are well fitted by a straight line ($r = 0.53$; $P < 0.01$).

The undiminished plasma progesterone levels after ovariectomy were not anticipated. A substantial percentage of plasma progesterone is contributed by the adrenals (9). A compensatory increase in progesterone secretion by the adrenals after ovariectomy could account for the apparently unchanged levels.

Discussion

We investigated the effect of exogenously administered progesterone in a peanut oil vehicle on halothane requirements in ovariectomized rabbits. We compared the results with results obtained in two control groups: 1) peanut oil-injected ovariectomized animals, and in 2) intact control animals. The progesterone-treated rabbits had significantly lower MAC values from the combined MAC values of the two control groups. The vehicle-treated group had a distribution of MAC values different from that in the intact group. The shape of the distribution of MAC values in the progesterone-treated animals was similar to that in the intact group. Interestingly, in the rat, GABA levels increase after ovariectomy and the increase is reversed by progesterone (5 mg/kg; 3 days) (14,15). Thus gabaaminergic mechanisms may help to explain the regulation of MAC by steroids.

Steroids act at both membrane and cytoplasmic sites in brain by mechanisms that include cyclic AMP formation, protein synthesis, ion conductance, and proteolytic cleavage (16–18). Majewska et al. (19) found that a 3α-hydroxy derivative of progesterone mimics the actions of barbiturate at the GABA receptor-chloride ion channel complex in brain tissue. Moreover, the steroid anesthetic, alphaxalone, at micromolar concentration potentiates Cl^- conductance increases mediated by receptor bound GABA and, at higher doses, activates, Cl^- conductance in the absence of GABA (20).

Progesterone levels in blood are thought to reflect progesterone levels in the brain (21). However, metabolites of progesterone may also contribute to effects on MAC, particularly if progesterone is administered chronically. The specific targets for these actions in brain and the time course over which they occur have not yet been identified.

Plasma progesterone concentrations (10–50 ng/ml) correlated with the degree of decrease in MAC (Fig. 2). Eight of the progesterone-injected animals had MAC values that were undiminished compared to the mean for vehicle injected controls 1.77 (group B). Three of these eight had atypically high plasma progesterone levels (60–90 ng/ml). Although blood levels can be indicative of brain levels, these high plasma progesterone levels could instead be a consequence of limited uptake by brain.

Plasma progesterone concentrations were sevenfold higher in the progesterone-treated group (37.33 ± 4.25 ng/ml) than in the control group. In our previous studies the ratio of plasma progesterone concentrations between pregnant and nonpregnant rabbits was 5:1 (5.5 ng/ml versus 1.67 ng/ml) (3,4). In humans the ratio of plasma progesterone in pregnant and nonpregnant individuals is about 60:1 (122 ± 8 ng/ml versus 2.3 ± 0.61 ng/ml) (6). With administration of exogenous progesterone in male dogs Tanifuji et al. (22) observed a 15% decrease in MAC of halothane when plasma progesterone levels increased six-fold (1.46 ± 0.22 ng/ml versus 8.9 ± 1.97 ng/ml). The difference in the progesterone values of the intact animals in our present study compared to the previous studies (3,4) might be related to cyclic changes of progesterone in rabbits (4–6 days cycle) (23). The higher MAC values in our control animals compared to those reported by Drummond (12) may be related to differences in technique.

Our results show that exogenously administered progesterone associated with plasma progesterone concentrations from 10 to 50 ng/ml decreases halothane MAC and that these plasma levels of progesterone are inversely correlated with MAC halothane (Fig. 2). These observations support the hypothesis that decreased MAC levels during pregnancy are a response to high progesterone levels. We suggest that increased plasma levels in general, and brain levels of progesterone in particular, affect the amount of anesthetic required to induce general anesthesia with halothane.

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Sixty-Five Years Ago In

Anesthesia & Analgesia

I. W. Magill: Technique in endotracheal anesthesia. Current Researches in Anesthesia and Analgesia: 1931;10:164–8.

Sir Ivan Magill (1888–1986) was a British anesthetist who was and is internationally recognized as a giant in the history of modern anesthesia. He was not the first to use endotracheal anesthesia. Nor was his claim to fame limited to his contribution to the development of endotracheal anesthesia. His persistent, vocal and ever so logical advocacy of endotracheal anesthesia, combined with superb skill as a laryngoscopist and intubationist, placed him in the forefront of those who so popularized endotracheal anesthesia that instead of being used only rarely and only by few, endotracheal anesthesia became so routine as to become today commonplace.

This 1931 paper reflects the fact that at that time endotracheal anesthesia was not being used as widely and frequently as it deserved to be. Magill reasons in this article that its lack of popularity was related to the fact that most anesthetists did not really understand how to go about intubating a patient. When they did try to intubate, all too often they either traumatized the patient's airway or teeth, or they angered the classically impatient surgeon of the '30s by taking too long to get the tube into the trachea. These problems could be readily resolved, Magill points out, if one but carefully analyzed details involved in tracheal intubation. Magill then sets out to describe how intubation can and should be done simply, rapidly and atraumatically. He speaks with the voice of authority. His introduction into full-time anesthesia was in 1919 at Queen Mary's Hospital for Facial and Jaw injuries where he was confronted by frightful anesthetic problems involved in the repair of gross facial trauma after four years of World War I. The first thing Magill emphasizes in this present article is the necessity for assuring that the head of the patient is in the correct "sniffing" position, or, as he put it, the position for a good draft of ale. He then goes on to describe proper use of a speculum (yes, a speculum: not a laryngoscope as we know it today). But this is necessary only if one insists on making intubation difficult by using the oral route. Much easier would be "blind intubation, through the nose, the most valuable maneuver in the whole technique". Indeed, in the days before neuromuscular relaxants really skilled anesthetists took pride in knowing how to do a blind nasotracheal intubation in even the most difficult cases swiftly, easily and almost casually. No need to make a production of it that today so often accompanies attempts at (and failures with) blind nasal intubation. Those who want perspective of the art and skill of intubation, especially blind nasal intubation, will enjoy this paper by the grandfather of tracheal intubation.

Failure of Proglumide, a Cholecystokinin Antagonist, to Potentiate Clinical Morphine Analgesia

A Randomized Double-Blind Postoperative Study Using Patient-Controlled Analgesia (PCA)

Klaus A. Lehmann, MD, PhD, Michaela Schlüsener, and Panagiotis Arabatsis

LEHMANN KA, SCHLÜSENER M, ARABATSIS P. Failure of proglumide, a cholecystokinin antagonist, to potentiate clinical morphine analgesia: a randomized double-blind postoperative study using patient-controlled analgesia (PCA). Anesth Analg 1989;68:51–6.

The potential clinical utility of drug interactions between morphine and the cholecystokinin antagonist proglumide was examined in 80 postoperative patients suffering from moderate to severe pain. Four groups of ASA I–III patients (mean age 51 years, mean weight 72 kg) recovering from major abdominal or gynecological surgery (mean duration of surgery 141 minutes) performed under balanced anesthesia (midazolam, droperidol, fentanyl, N_2O, enflurane) were randomly assigned to self-administer morphine–proglumide mixtures on the first postoperative day (ODAC; morphine demand dose 3 mg; infusion rate 0.36 mg/hr; lockout time 2 minutes; hourly maximum dose 15 mg/hr; proglumide doses per demand 0, 50 μg, 100 μg, or 50 mg). Morphine consumption, actual as well as retrospective pain scores (0–5) and side effects were evaluated. Mean duration of patient-controlled analgesia (PCA) in the subgroups was 17–19 hours, during which time 24.6 ± 9.5 to 28.0 ± 3.4 μg morphine·kg^{-1}·hr^{-1} was given. There were no statistically significant differences between the groups either for drug consumption, pain scores, or side effects. It is therefore concluded that proglumide does not potentiate morphine analgesia in a clinical (postoperative) setting.

Key Words: ANALGESICS—morphine. DRUG INTERACTIONS—cholecystokinin, proglumide. PAIN, POSTOPERATIVE—patient-controlled analgesia.

Important progress has been made in understanding pain transmission and processing. Since the discovery of specific opiate receptors and their physiologic agonists (endorphins, enkephalins), there is now no doubt that centrally acting analgesics mimic and potentiate the effects of the endorphinergic neurotransmitter system. Main sites of action are synapses along the ascending pain tracts (direct suppression of transmission) as well as those in central nuclei where inhibitory signals are generated which reach the spinal cord via descending pathways. It has also been shown in a number of studies that local or systemic application of endorphins produces analgesic effects comparable to those of typical opiate drugs.

A recent issue is whether the organism not only produces agonists for the opiate receptors (i.e., endorphins) but also physiologic antagonists. Cholecystokinin-like peptides, which are known to be gastroenteric hormones as well as central neurotransmitters, seem to be suitable candidates as endorphin antagonists. If they themselves could be antagonized, the result should be an increased efficacy of the endorphinergic system. Thus it has been reported by Watkins et al. (1) that proglumide, a cholecystokinin antagonist, potentiates morphine analgesia in rats. These results were confirmed by Price et al. (2) with human volunteers; only a narrow range of proglumide concentrations, however, proved to be effective.

The aim of the present study was to investigate proglumide–morphine interactions in subjects with moderate to severe postoperative pain. For this purpose patients self-administered small IV morphine dosages to which varying amounts of proglumide

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Address correspondence to Dr. Lehmann, Institut für Anaesthesiologie der Universität zu Köln, Joseph-Stelzmann-Strasse 9, D-5000 Köln 41, Federal Republic of Germany.

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Table 1. Patients and Anesthesia*

Group†	Sex (male/female)	Age (yrs)	Weight (kg)	Duration of anesthesia (min)	Interval extubation-PCA-start (min)
Placebo	7/13	53.5 ± 10.4	71.3 ± 9.2	140.0 ± 42.0	70.5 ± 66.5
50 μg	4/16	49.9 ± 12.9	69.4 ± 8.5	128.2 ± 24.0	45.1 ± 35.0
100 μg	8/12	50.4 ± 11.3	75.4 ± 11.7	149.5 ± 37.4	58.3 ± 69.7
50 mg	9/11	49.8 ± 11.2	74.8 ± 9.0	145.7 ± 46.1	53.1 ± 30.5

*Values are means ± SD.
†Amount of proglumide administered with every 3 mg morphine given using a patient-controlled analgesia pump.

were added (patient-controlled analgesia, PCA). Morphine consumption during the first 20 postoperative hours and analgesic efficacy were measured, as were postoperative circulation, respiration, and side effects.

Patients and Methods

Patients. Following institutional approval and written informed consent, 80 patients, ASA physical status I–III, undergoing elective major gynecologic or abdominal surgery of at least 100 minutes duration, gave informed consent to participate in an investigation with the On-Demand Analgesia Computer (ODAC). Exclusion criteria were drug abuse and pregnancy as well as diseases of the respiratory or excretory organs. Patients were randomly assigned in a double-blind fashion to four study groups.

Anesthesia. Patients were premedicated using 10 mg diazepam orally on the evening before surgery. Intravenous induction of anesthesia was performed with midazolam (5 mg), droperidol (2.5 mg), atropine (0.5 mg), pancuronium (4 mg), and fentanyl (5 μg/kg). After tracheal intubation following succinylcholine (1 mg/kg), patients were ventilated to normocapnia using nitrous oxide (70%) in oxygen; fentanyl (0.1 mg), or pancuronium (0.5–1 mg) were administered as needed; on clinical signs of inadequate anesthesia low enflurane concentrations (0.5 vol.%) were given for short periods of time. Neuromuscular blockade was antagonized at the end of surgery using neostigmine (1 mg) and atropine (0.5 mg). Opiate antagonists were not given.

Postoperative pain treatment. Patients were connected to a PCA pump (On-Demand Analgesia Computer, ODAC) as soon as possible after extubation. The morphine demand dose was 3 mg (lockout time 2 minutes; continuous infusion rate 0.36 mg/hr; hourly maximum dose 15 mg/hr). Proglumide was added to the morphine so that patients received additional 0 mg (group 1 = placebo), 0.05 mg (group 2), 0.1 mg (group 3), or 50 mg proglumide (group 4), along with every 3 mg morphine. After further explanation of the machine patients followed normal ward routine until the next morning. During this period, sedatives and additional analgesics were not permitted.

Measurements. Blood pressure, heart rate, respiratory frequency, and pain scores (0: no pain, 1: sometimes moderate, 2: always moderate, 3: sometimes severe, 4: always moderate + sometimes severe pain, 5: discontinuation due to inefficacy) were monitored hourly up to 480 minutes after PCA start. On the following day all patients were questioned in standardized interviews (retrospective pain score [0–5], PCA acceptance, side effects). Hourly and cumulative morphine dosages were calculated from the time points of valid demands.

Arithmetic means, standard deviations, and medians were calculated for statistical evaluation; groups were compared by means of the Mann-Whitney-Wilcoxon and Kruskal-Wallis tests for independent samples (level of significance $P = 0.05$).

Results

Demographic data of the 28 male and 52 female patients are listed in Table 1. There were no statistically significant differences between the groups with respect to age, weight, duration of anesthesia, and time between extubation and start of PCA. Types of surgery were also comparable in all groups; most interventions were major abdominal ($n = 59$; mostly cholecystectomies, $n = 20$; and gastric surgery $n = 16$); 19 of 21 major gynecologic interventions were hysterectomies. Figure 1 shows cumulative dose–time plots for the 20 patients in group 1. Similar individual variability in drug consumption was also observed in the other groups. Figure 2 displays the

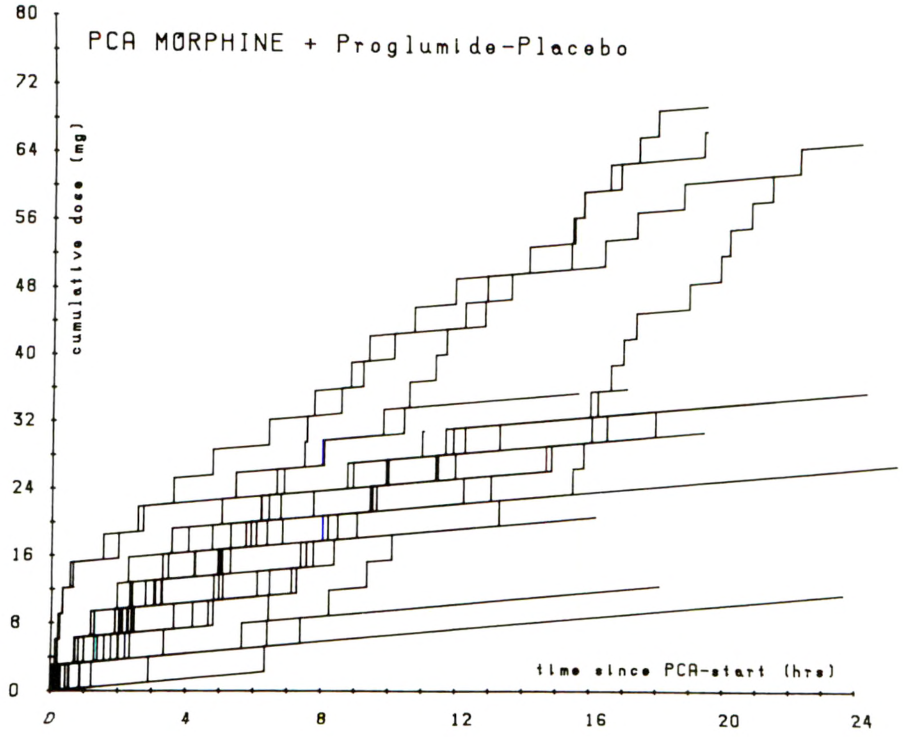

Figure 1. Cumulative dose–time plots (group 1, no proglumide). Each step is indicative of a patient demand (3 mg morphine); curves gradually rise due to continuous infusion (0.36 mg morphine/hr).

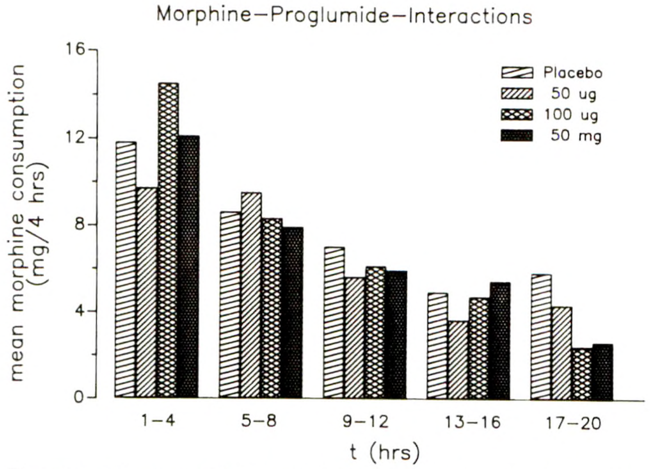

Figure 2. Mean morphine requirements in 4-hourly observation periods in the different treatment groups.

mean morphine dosages required during each 4-hourly observations. Dosages generally decreased with time; there were no important differences between the groups. Table 2 shows duration of PCA treatment, number of demands, as well as morphine and proglumide consumption ($\mu g \cdot kg^{-1} \cdot hr^{-1}$); there were no statistically significant differences between the groups, either. Mean proglumide intake, calculated for 20 hours treatment and 70 kg patient weight, was 0, 0.57, 1.2, and 582 mg for groups 1–4, respectively. Figure 3 displays actual pain scores during the first 8 PCA hours (Kruskal-Wallis: no significant differences). Table 3 lists mean retrospective pain scores (questioned on the following day after termination of PCA) as well as data of patient acceptance. Again, no statistically significant differences between the groups were found. PCA provided acceptable pain relief in all cases. Fifty to eighty percent of patients who had experience with earlier conventional postoperative pain treatment preferred self-administration, and 15–25% would have liked to remain connected to the PCA apparatus at the end of the observation period. Personal care by the nursing staff would have been chosen by only 5–10% of the patients.

Postoperative circulatory and respiratory status was normal in all groups; Figure 4 displays mean respiratory frequencies during the first 8 PCA hours (no significant differences). Table 4 lists the most important side effects: in general, they are typical in type (nausea, emesis, sweating, micturition problems) and incidence to the well known side effects in the immediate postoperative period. Again, all groups were statistically quite comparable.

Discussion

Patient-controlled analgesia is an accepted method for improving postoperative (acute) pain treatment. One of the most important results of PCA studies is the objective documentation of a tremendous individ-

Table 2. Patient-Controlled Analgesia (PCA)

Group†	Duration of PCA (hrs)	Total number of demands	Demands per patient	Morphine consumption (μg$\cdot$kg$^{-1}\cdot$hr^{1})	Proglumide consumption (μg$\cdot$kg$^{-1}\cdot$hr^{1})
Placebo	18.7 ± 4.1	195	9.7 ± 5.6	28.0 ± 13.4	0
50 μg	18.2 ± 1.8	160	8.0 ± 3.9	24.6 ± 9.5	0.4 ± 0.2
100 μg	17.0 ± 3.5	186	9.3 ± 5.0	27.7 ± 13.1	0.9 ± 0.4
50 mg	17.8 ± 2.9	175	8.6 ± 4.8	25.0 ± 12.7	416.7 ± 211.7

*Values are means ± SD.
†Amount of proglumide administered with every 3 mg morphine given using a patient-controlled analgesia pump.

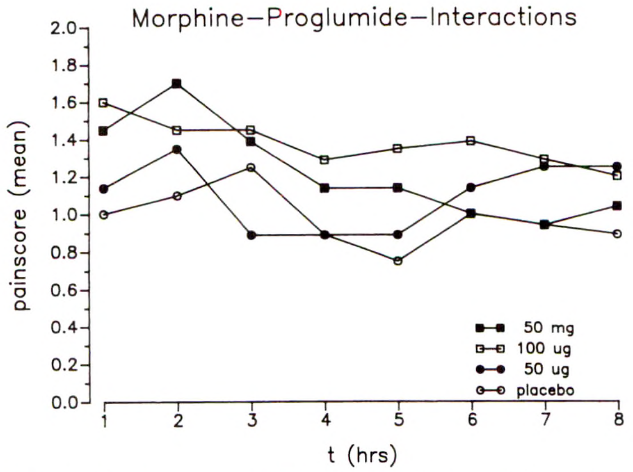

Figure 3. Mean pain scores during the first 8 hours of observation.

ual variability in analgesic demands, which was again confirmed in the present paper (Figure 1). Less recognized among anesthesiologists is the fact that PCA has also become the standard of reference for pharmacologic investigations to establish, for example, analgesic equipotency ratios (3), the relation between pharmacokinetic and dynamic findings (4), or the importance of drug interactions (5).

The gastroenteric hormones, gastrin, caerulein, and cholecystokinin are chemically related proteins with a similar C-terminal pentapeptide fragment. Their effects on digestion have been recognized for a long time. Cholecystokinin (CCK) stimulates the pancreas (calcium efflux, glucose uptake, amylase secretion), enhances gall bladder contraction, and inhibits gastric mobility. It is commonly accepted that CCK exerts its effects via specific receptors within the gastrointestinal tract; CCK-sensitive cells are present in the gall bladder, stomach, pancreas, and various parts of the intestine (6). Cholecystokinin also inhibits food intake, which implies the presence of additional central sites of action (7) Gaudreau et al. (8) identified specific CCK receptors in various areas of the brain; the distribution suggested an influence of CCK on food intake, sensoric processes, and emotion. Interactions with CNS dopamine are thought to dominate in the midbrain, while GABA interactions seem to be important in cortical areas (9,10).

In vivo experiments with cholecystokinin have led to contradictory results. Following intraventricular injections, a reduction of global explorative activity was found in rats (11); very high subcutaneous dosages produced sedation and naloxone-reversible analgesia in mice (12). Faris et al. (13), on the contrary, described antagonism of opiate-induced analgesia in rats. This finding was underlined by the observation that intraventricular or intrathecal injection of antibodies against CCK octapeptide delayed the development of tolerance to analgesia induced by morphine or electroacupuncture in rats (14,15). It was concluded from such results that endogenous cholecystokinin acts as a physiologic endorphin antagonist and that the balance between these neurotransmitter systems determines an individual's susceptibility to pain; opiate tolerance thus could possibly be discussed as a predominance of the CCK system.

Proglumide (DL-4-Benzamido-N,N-dipropylglutaric acid, Milid), as well as the cyclic nucleotid dibuturyl-c-GMP and the tryptophane derivative benzotript, are members of a series of drugs that are thought to be specific cellular surface antagonists for cholecystokinin and related peptides (16). Proglumide has been used for some time in the treatment of peptic ulcerative disease because it inhibits gastrin-stimulated secretion of gastric acid; furthermore, it blocks CCK-mediated gall bladder contraction as well as pancreatic secretion. The effects of proglumide on the central nervous system are unclear. Gaudreau et al. (8) were unable to demonstrate blockade of central CCK receptors even with relatively high doses of proglumide. Eward and Wingate (17) found that proglumide did not antagonize CCK-mediated vagal stimulation in rats. Chiodo and Bunney (9), on the other hand, observed inhibition of excitatory effects induced by iontophoretically applied cholecystokinin to dopaminergic neurons in the midbrain; Sheehan and de Belleroche (10) found similar interactions concerning the GABA release from cells in the pari-

Table 3. Analgesia and Patient Acceptance

Group*	Retrospective painscore (mean ± SD)	Comparison of present PCA with earlier experience (%)			Wish to remain connected to PCA pump (%)			Nurse preferred instead of PCA (%)
		(+)	(=)	(−)	(+)	(=)	(−)	
Placebo	1.04 ± 0.68	54.5	45.5	0	15	30	55	10
50 μg	1.10 ± 0.64	60	30	10	15	35	50	10
100 μg	1.39 ± 0.99	83.3	8.3	8.4	25	55	20	10
50 μg	1.29 ± 0.92	81.8	18.2	0	20	50	30	5

*Amount of proglumide administered with every 3 mg morphine given using a patient-controlled analgesia pump.
(+) better/positive, (=) comparable/uncertain, (−) worse/negative.

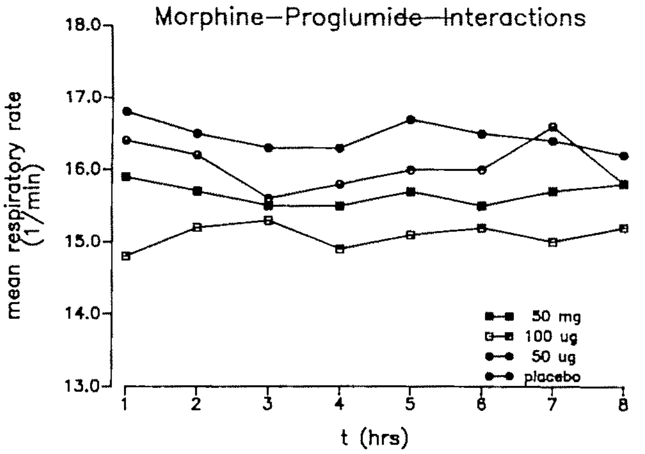

Figure 4. Mean respiratory frequencies during the first 8 hours of observation.

etal cortex. The CCK-mediated reduction of global explorative activity in rats was clearly antagonized by proglumide (11).

Few investigations have addressed the question as to whether proglumide interferes with the possible antianalgesic effects of cholecystokinin. There is evidence from biochemical studies that proglumide acts not only as a specific CCK receptor antagonist, but also inhibits the metabolic degradation of endorphins (18). In addition, Rezvani et al. (19) speculated that intensification of opiate analgesia by proglumide could be explained by a direct stimulation of endorphinergic δ-receptors.

Tang et al. (20) found in in-vivo experiments that proglumide counteracted the development of acute spinal opiate tolerance. Similar observations, again with rats, were made by Watkins et al. (1) who found that systemic or intrathecal administration of proglumide not only antagonized preexisting tolerance to morphine but also enhanced, in nontolerant animals, endogenous (footshock) as well as exogenous (morphine-) analgesia. Price et al. (2) confirmed these findings with human volunteers using experimental pain techniques (thermal skin stimulation in the range of 45–51°C). In their experiments, IV morphine 0.04 mg/kg failed to produce measurable analgesia, but significant analgesia could be obtained using a combination of morphine 0.04 mg/kg and proglumide 100 μg (given 5 minutes after the morphine). Even better effects were found for the combination of morphine 0.06 mg/kg and proglumide 50 μg, whereas no potentiation was observed using morphine 0.06 mg/kg and proglumide 100 μg. Single doses of proglumide 100 μg or the combination of morphine 0.04 mg/kg and proglumide 10 μg proved to be analgetically ineffective. Taking a volunteer's body weight of 70 kg, the effective dose range (micrograms proglumide per milligram morphine) thus was in the range of 11.9 to 35.7.

A comparable dose range was also used in the present study (groups 2 and 3: 50 to 100 μg proglumide per 3 mg morphine). Group 1 (placebo) patients did not receive any proglumide while group 4 patients were given a high dose, 50 mg per 3 mg morphine. It was the aim of this investigation to find out whether the postulated potentiation of morphine analgesia by proglumide could lead to a reduction of clinically needed morphine consumption or to improved analgetic efficacy. Our results clearly show that neither statistically significant nor clinically relevant proglumide–morphine interactions in the wide dose range studied occurred: this is equally true if one regards actual and retrospective pain scores or morphine consumption.

Reasons for the discrepancy between our study and the findings by Price et al. (2) remain unclear. Obviously, the subjects studied were quite different: Price et al. (2) worked with healthy volunteers 20 to 40 years old who were virtually pain-free, while the patients of the present investigation were mainly elderly, had undergone major surgery, and suffered from clinical pain requiring treatment. In any event, our results underline that data obtained in studies of experimental pain must not be transferred uncritically to the clinical situation.

On the other hand, the morphine consumption

Table 4. Side Effects (%)

	Nausea			Sweating		
Group	Minor	Major	Vomiting	Minor	Major	Micturition difficulties
Placebo	15	5	10	15	0	10
50 μg	10	5	5	5	5	0
100 μg	35	10	10	15	10	0
50 mg	5	10	10	10	0	0

*Amount of proglumide administered with every 3 mg morphine given using a patient-controlled analgesia pump.

(Table 2) as well as the mean retrospective pain scores (Table 3) confirm our previous results with postoperative PCA where morphine demand doses of 2 mg were used (21). Patient acceptance and side effects, too, were quite comparable to the earlier findings. Thus, any effect of proglumide in the dose range studied on analgesic actions of morphine can be excluded (Table 4, Fig. 4).

In conclusion, the present study could not confirm, in a clinical setting, the existence of theoretically interesting hypothetical interactions between the cholecystokinin antagonist proglumide and morphine. Patient-controlled analgesia proved to be effective and safe for the relief of postoperative pain; for conventional management of postoperative pain the pronounced individual variability in postoperative analgesic demands that are clearly documented here should more often be taken into account.

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Clinical Reports

Neuroleptanalgesia Using Alfentanil for Awake Craniotomy

Eric C. Welling, MD, and Judith Donegan, MD, PhD

Key Words: ANALGESICS—alfentanil. ANESTHESIA—neurosurgical. ANESTHETIC TECHNIQUES—neurolept.

Intracranial surgical procedures in which there is a risk of iatrogenic injury to speech, memory or motor areas may necessitate the patient's cooperation. Electrocorticography and observation of patient response to direct electrical stimulation of the cerebral cortex are used to define the boundaries of these vital areas. Drugs administered during the course of the anesthetic must help to maintain patient comfort but must not unduly depress ventilation or interfere with electroencephalographic identification of seizure foci. A neuroleptanalgesic technique, combining fentanyl or sufentanil with droperidol, is frequently employed [1]. Because alfentanil has a more rapid onset and shorter duration of action, we felt that it might offer advantages over fentanyl and sufentanil. We describe its use in four consecutive patients undergoing resection of epileptogenic foci.

Case Reports

Case 1

A 29-year-old 65 kg female presented for excision of an epileptogenic focus in her left temporal lobe, demonstrated by the Wada test [2] to be the site of her speech and memory centers. The patient received no preoperative medication. After intravenous and arterial catheters were inserted, the patient was positioned in the right lateral decubitus position. Arterial blood while breathing room air had a pH of 7.4, a Pco_2 of 38 mm Hg, and a Po_2 of 94 mm Hg. A nasal cannula for delivery of oxygen was placed. Other monitors included a precordial stethoscope placed so as to obtain good breath sounds and heart tones, a pulse oximeter, a skin probe for measuring temperature and an electrocardiogram. A small plastic catheter was connected to the collection line of the mass spectrometer; this catheter was adjusted so that it protruded just beyond the nasal cannula into one nostril and was used for monitoring the trend of exhaled CO_2. Droperidol, 2.5 mg IV, and alfentanil 5 μg/kg were administered and an alfentanil infusion started at 1.5 μg/kg/min. A 5 μg/kg bolus was given every 2–3 minutes to a total dose of 20 μg/kg, at which time the patient was sedated, breathing spontaneously, and comfortable. During peak periods of stimulation (i.e., skin infiltration with local anesthetic, drilling and sawing bone, and turning the bone flap) the alfentanil infusion was increased and/or a 5 μg/kg bolus was repeated, additional droperidol was given, and 50% nitrous oxide was added to the oxygen being administered via the nasal cannula. During this time, verbal communication was maintained with the patient. Anesthetic requirements were determined by complaints of pain and the adequacy of ventilation and oxygenation as asessed by precordial stethoscope, pulse oximeter, mass spectroscopy, and arterial blood gases. Arterial blood gases at the time of turning the bone flap, with the patient breathing $N_2O:O_2$ 50:50, were pH 7.29, Pco_2 57 mm Hg, Po_2 92 mm Hg.

During cortical mapping, the alfentanil infusion was reduced to 0.5 μg/kg/min and within 2 minutes the patient was alert, cooperative, and without complaints of pain. Cortical mapping consisted of electrocorticography for localization of the seizure focus and determination of the borders of the speech and motor areas of the cortex by having the patient move, speak, and identify objects during cortical stimulation. In an

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Address correspondence to Dr. Donegan, Department of Anesthesia, Box 0648, University of California–San Francisco, San Francisco, CA 94143.

effort to ensure identification and resection of all seizure foci, the patient was given etomidate 6 mg and within 30 seconds developed a focal seizure [3]. During the seizure, the patient maintained an adequate airway, did not vomit, and had a respiratory rate of 10 breaths/min. Fifteen minutes later, an arterial blood sample drawn with the patient breathing $N_2O:O_2$ 50:50 was pH 7.27, Pco_2 54 mm Hg, Po_2 83 mm Hg. The depth of anesthesia was deepened by increasing the rate of the alfentanil infusion to 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a partial left temporal lobectomy was performed. Upon conclusion of the lobectomy, the alfentanil infusion rate was decreased to 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and electrocorticography was repeated to ensure complete resection of the seizure focus. During closure, the alfentanil infusion was maintained at 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until 15 minutes before the end of surgery, when it was discontinued. The patient responded to commands and was pain free at the completion of surgery, at which time pH was 7.32, $Paco_2$ 40 mm Hg, and Pao_2 115 mm Hg. Thirty minutes after arrival in the recovery room, arterial blood pH was 7.33, Pco_2 42 mm Hg, and Po_2 100 mm Hg while breathing room air. During the 6.5-hour procedure a total of 33,340 μg alfentanil (513 μg/kg) and 20 mg droperidol (0.31 mg/kg) were administered.

Case 2

A 36-year-old, 110 kg female presented for partial right temporal lobectomy for a history of partial complex seizures. Electroencephalography localized the seizure focus to the right temporal lobe, and a Wada test demonstrated bilateral localization of her speech center. Although the patient was obese, she was very active and had no evidence of respiratory abnormalities. Bolus doses and infusion rates of alfentanil were administered on the basis of lean body weight, estimated to be 75 kg. Monitors employed in this and the subsequent cases were the same as those used for case 1 with the exception of an intraarterial catheter. Each patient had a cannula placed for the administration of oxygen and N_2O and in each case the neuroleptanalgesia was supplemented by injection of local anesthetics by the surgeon. After positioning, droperidol, 2.5 mg, and alfentanil, 7.5 μg/kg, were administered and an alfentanil infusion was begun at 0.5 μg/kg/min. During periods of peak stimulation alfentanil, 7.5 μg·kg, was given as a bolus or the infusion was increased to 1.0–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. When patient cooperation was necessary the infusion was reduced to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This produced an alert, cooperative, comfortable patient within 2 minutes. The subtotal temporal resection was uneventful, and the patient was awake at the completion of the procedure. Throughout the seven hour procedure the patient maintained a respiratory rate of 8–12 breaths/min and an arterial oxygen saturation (Sao_2) $\geq$ 95%. A total of 25,000 μg alfentanil (333 μg/kg lean body weight; 227 μg/kg actual body weight) and 36 mg droperidol (0.33 mg/kg actual body weight) were administered.

Case 3

An 18-year-old, 64 kg male underwent a partial left temporal lobectomy for a history of partial complex seizures. A Wada test demonstrated his speech center to be ipsilateral to the seizure focus. Because the patient had a history of syncope secondary to sick sinus syndrome, a temporary pacemaker was placed preoperatively. Droperidol, 2.5 mg, and alfentanil bolus injections of 5, 5, and 7.5 μg/kg were administered over 15 minutes until the patient was sedated, at which time an alfentanil infusion was started at 0.5 μg/kg/min. Subsequently the rate of infusion was varied from 0.25 μg/kg/min when electrocorticography was being performed to 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during periods of peak stimulation. Total drugs administered during this 7.5-hour anesthetic were alfentanil, 28,000 μg (438 μg/kg), and droperidol, 25 mg (0.39 mg/kg). It was not necessary to use the pacemaker as there were no perioperative episodes of bradycardia.

Case 4

A 14-year-old, 57 kg male was scheduled for excision of a right parietal lesion that was consistent with a brain tumor on magnetic resonance imaging (MRI) scan. He had a history of seizures since age six months, well controlled until two months before admission. Bilateral speech distribution was demonstrated on preoperative testing. Droperidol, 2.5 mg, and alfentanil, 5 μg/kg, were administered and an alfentanil infusion started at 1.0 μg/kg/min. Prior to skin infiltration an additional 5 μg/kg bolus was given and the infusion increased to 1.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The brain was found to be "tight" as the dura was opened. Sufficient cerebral relaxation was not obtained by decreasing the rate of alfentanil infusion and encouraging the patient to breathe deeply; therefore, an indwelling urinary catheter was inserted and mannitol, 1 g/kg, was administered with good results. When cortical mapping was to be performed, the alfentanil infusion was decreased to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and within 2 minutes the patient was awake, cooperative and comfortable. During the procedure the respiratory rate was >14/min and Sa_{O_2} >97%. Alfentanil, 19,650 μg (345 μg/kg), and droperidol, 12.5 mg (0.22 mg/kg), were administered over 5.5 hours.

Discussion

Anesthesia for the resection of epileptogenic foci has varied from local to general endotracheal with intraoperative awakening during electrocorticography [4,5]. The combined use of a major tranquilizer and a potent analgesic to produce a state of indifference, immobility, and analgesia, termed neuroleptanalgesia, has been widely employed [1]. Tasker and Marshall [6] demonstrated that with careful titration of the agents the patient could be maintained in a comfortable state but able to ventilate adequately and to verbalize and obey commands. A combination of droperidol and fentanyl or sufentanil supplemented by injection of local anesthetics by the surgeon has been a commonly used technique at many institutions, including ours.

Alfentanil has central nervous system effects similar to those of fentanyl and sufentanil, causing an increase in the number of low frequency, high amplitude delta waves on the EEG [7] without affecting seizure foci. Studies evaluating recovery by means of tests designed to measure psychomotor function (e.g., coordination and ability to concentrate) suggest that patients recover more rapidly from alfentanil than from fentanyl-supplemented anesthesia [8]. Clinically, alfentanil has a more rapid onset and a shorter duration of action than either fentanyl or sufentanil. The basis for these differences in clinical effect resides in the physicochemical and pharmacokinetic differences between alfentanil, fentanyl, and sufentanil [9–11], as summarized in Table 1. The relatively high percentage of unionized drug and moderate lipid solubility of alfentanil cause it to equilibrate rapidly across the blood:brain barrier and thus to have a rapid onset of action. The high degree of protein binding and moderate lipid solubility result in limited tissue binding and a small volume of distribution. These characteristics are associated with a relatively short duration of action. Thus, alfentanil may be administered more easily in small, fractional doses than other narcotics, such that the desired effects can be achieved during procedures that require rapidly changing levels of consciousness.

Table 1. Comparison of Physicochemical and Pharmacokinetic Properties of Alfentanil, Fentanyl, and Sufentanil

Property	Alfentanil	Fentanyl	Sufentanil
Percent unionized	89	8.5	20
Octanol:water partition coefficient	129	816	1727
Percent protein bound	92	84	93
Volume of distribution L/kg	0.8–1.0	4.0	1.7–2.9
Clearance ($ml \cdot kg^{-1} \cdot min^{-1}$	6–8	13–14	11–13
Elimination half-life (min)	94	219	148–164
Plasma concentration for spontaneous ventilation (ng/ml)	100–200	2–5	—

Respiratory depression in neurosurgical patients is an important issue because elevated Pa_{CO_2} values produce an increase in cerebral blood volume, thereby worsening brain protrusion. Because patients having surgery for epilepsy are "awake" they cannot be passively hyperventilated, and because urinary catheters are not routinely employed, diuretics cannot be administered to decrease cerebral volume. Previous studies of neuroleptanalgesic techniques using fentanyl reported levels of ventilatory depression (Pa_{CO_2} 45–60 mm Hg) [12] similar to what we measured in one patient given alfentanil. The effects of alfentanil and droperidol in combination have not been studied in neurosurgical patients; however, the ventilatory depressive effects of fentanyl do not appear to be increased by the addition of droperidol [12]. A dose-dependent ventilatory depression with clinically useful doses of fentanyl and droperidol occurs within 5 minutes and lasts from 30 minutes to 4 hours depending on the dose of fentanyl. Equianalgesic doses of alfentanil may cause respiratory depression of shorter duration and less chest wall rigidity than are produced by fentanyl [8,13,14]. Plasma alfentanil levels associated with spontaneous ventilation [15] have been defined as shown in Table 1, although there exists wide interindividual variability [16]. We measured arterial blood gases only in the first patient in whom we used the technique. We have not inserted arterial catheters in previous patients who received fentanyl or sufentanil for the same surgical procedure, partly for patient comfort but also because these are relatively young, otherwise healthy patients with normal intracranial compliance. Breath sounds and arterial saturation are continuously monitored as is the trend of exhaled CO_2; verbal communication is maintained and the ability of the patient to take a deep breath on command is frequently assessed. After the initial case in which alfentanil was used, it was decided to proceed with our routine monitors in the absence of an arterial catheter and this has subsequently proved to be satisfactory. However, in older patients or those with pulmonary abnormalities or decreased intracranial compliance it would be advisable to measure arterial blood gases frequently whenever administering alfentanil or any drug that may depress respiration.

In summary, it is our experience that intravenous alfentanil, because of its relatively rapid onset of effect and short duration of action, is more easily administered to achieve the changing levels of awareness and cooperation required in "awake" patients undergoing resection of epileptogenic foci than either fentanyl or sufentanil. Patients did not develop chest wall rigidity, apnea, or hypoxia; they took deep breaths on command throughout the duration of alfentanil infusion. The four patients we report were alert upon arrival in the recovery room and, when questioned, stated they had been comfortable intraoperatively. Because of the potential danger of respiratory depression associated with the use of narcotics, frequent arterial blood gas measurements should be performed during the intraoperative and postoperative period whenever alfentanil or another narcotic is administered to a patient with abnormal pulmonary function or elevated intracranial pressure.

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Unilateral Horner's Syndrome Associated with Interpleural Catheter Injection of Local Anesthetic

Stephen K. Parkinson, MD, James B. Mueller, MD, Thomas J. Rich, MD, and William L. Little, DO

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—interpleural. PAIN, POSTOPERATIVE—interpleural local anesthetic.

Interpleural regional analgesia is a relatively new technique the exact mechanism of which remains to be elucidated (1). A recent case report suggests splanchnic nerve blockade may be associated with interpleural catheter analgesia (2). We report two cases of unilateral upper thoracic sympathetic blockade with resultant Horner's syndrome and upper extremity sympathetic denervation.

Case 1

A 31-year-old man with atypical chest pain of 2 years' duration was seen in our pain clinic. His pain, constant and stabbing in nature, was most prominent in the left axilla with radiation anteriorly to the breast. He also complained of intermittent burning and throbbing in his left arm and shoulder. Extensive cardiac, pulmonary, rheumatologic, and neurologic evaluations were unremarkable, including chest roentgenogram, bone scan, CT scan, myelogram, stress ECG, echocardiography, and nerve conduction/electromyographic studies. Previous trials of tricyclic antidepressants, nonsteroidal antiinflammatory agents, and transcutaneous electrical nerve stimulation were of little benefit.

After obtaining informed consent, we performed a left stellate ganglion block (using 15 ml of 0.5% lidocaine/0.125% bupivacaine with 1:400,000 epinephrine) for diagnostic as well as possible therapeutic purposes. The block resulted in a 4°C increase in the left index finger skin temperature and a left Horner's syndrome. The arm and shoulder pain immediately improved, but the axillary and anterior chest pain remained.

At his next visit it was found that his arm and shoulder pain relief lasted 4–5 hours after the stellate block and then returned to baseline. His predominant pain continued to be that in the left axilla and the left anterior chest. Because the chest pain apparently worsened with sneezing and coughing (possibly pleuritic?), we elected to try interpleural analgesia. Interpleural analgesia for postoperative pain control in cholecystectomy and nephrectomy patients is commonly employed at our institution, so we felt comfortable in offering this to our patient.

Informed consent was obtained, an IV was started, and 500 ml of lactated Ringer's solution given before injection of the local anesthetic. A left interpleural catheter was inserted using the technique described by Reiestad and Strömskag (3), except that instead of a Tuohy needle, we used an 18-gauge, thin wall, 5 cm Potts-Cournand needle with an obturator (Fig. 1), discarding the inner cutting needle and replacing it with the blunt obturator. After placement of the needle in the interplural space and with the needle positioned so the bevel was facing the visceral pleura, the obturator was removed and a 20-gauge epidural catheter was threaded through the remaining outer needle. The patient was then placed supine, with the bed in 15° head-down position to facilitate spread to the upper thoracic area. Twenty milliliters of 0.5% bupivacine with 1:200,000 epinephrine were injected over 1 minute. Within 15 minutes the patient noted drooping of his left eyelid and an increase in skin temperature in his left arm. After 30 minutes he had decreased sensation (although not complete anesthesia) from T-2 to T-8 on the left side and sympathetic denervation of his left arm (skin temperature 4°C

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Address correspondence to Dr. Parkinson, Department of Anesthesiology, Naval Hospital, Portsmouth, VA 23708.

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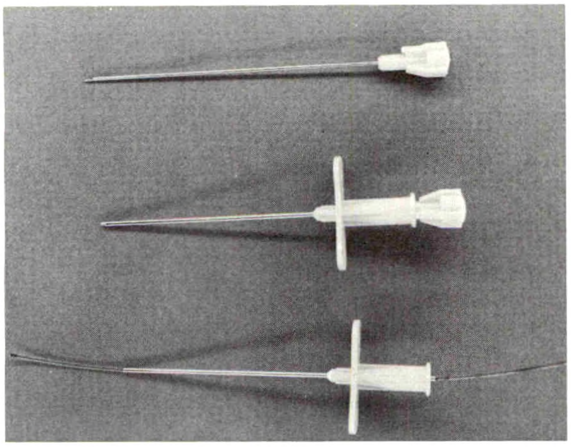

Figure 1. Potts-Cournand 18-gauge, thin wall needle used for placement of an interpleural catheter with inner cutting needle (top) removed and the blunt obturator inserted (middle). A 20-gauge epidural catheter fits through the needle once the obturator is removed (bottom). If the needle length (5 cm or 2⅛ inch) is insufficient then a standard epidural needle is used.

higher on left index finger than right index finger), as well as a left Horner's syndrome. Sensory and motor function of the left upper extremity remained intact, except for the area innervated by T-2 in the axilla which had decreased sensation. Vital signs remained unchanged. After 30 minutes he was taken out of the Trendelenburg position. The block provided 80% pain relief that lasted for several days. Another interpleural block was performed 1 week later, with the same development of evidence of upper thoracic sympathectomy, which again brought an element of relief for several days. After the two blocks, his pain returned to 30–40% of his baseline. He continues with moderate, but controllable pain and plans to return for repeat interpleural catheter injections if his pain worsens.

Case 2

An 11-year-old, 32 kg boy with short bowel syndrome was taken to surgery for cholecystectomy due to symptomatic cholelithiasis. The cholecystectomy was performed uneventfully under general endotracheal anesthesia. Before discontinuation of inhalation anesthetics and reversal of the muscle relaxant, the patient was placed in the left lateral decubitus position, and an interpleural catheter was placed in a manner similar to that described in case 1. The patient was made apneic prior to needle placement at the T-6 level approximately 8 cm from the midline. Ten milliliters of 0.5% bupivacaine with 1:200,000 epinephrine were injected through the catheter over 1 minute, with the patient in the supine position. A right Horner's syndrome and increased skin temperature of the right hand were noted in the postanesthetic recovery room and, subsequently, shortly after each injection through the catheter with 10 ml of 0.5% bupivacaine with 1:200,000 epinephrine.

Discussion

Sympathetic innervation to the head, neck, and upper extremity arises from the spinal cord at T-1–T-8. The sympathetic chain in the upper thorax lies on the posterolateral aspect of the vertebral bodies separated from the pleural cavity only by the parietal pleura. This apparently was the location and mechanism (diffusion through the parietal pleura) of the sympathectomies seen in these patients. When posttraumatic or postoperative patients are given interpleural injections of local anesthetics for relief of pain, they are generally maintained in a supine position for 20–30 minutes to allow better spread to the mid- and lower thoracic dermatomes. A Horner's syndrome has not been reported in the literature to date from the routine dosing of interpleural catheters. Placing our adult patient in the Trendelenberg position was perhaps what made the difference, allowing for better soaking of the upper thoracic (interpleural) cavity.

In summary, these two case reports substantiate the finding that interpleural injection of 0.5% bupivacaine can result in unilateral upper thoracic sympathectomy, as evidenced by the Horner's syndrome and upper extremity sympathectomy seen in both patients. The relationship of the thoracic sympathetic chain with the parietal pleura and the vertebral bodies remains relatively constant throughout the course of the thorax. It is likely that mid- and lower thoracic sympathetic denervation occurs routinely with interpleural injection of local anesthetics. This sympathetic denervation may be related to the efficacy of interpleural analgesia in the management of certain types of intraabdominal pain.

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Effect of Increased Intra-Abdominal Pressure during Laparoscopy on the Lower Esophageal Sphincter

Michael J. Jones, BSc, MRCP, FFARCS, Robin W. Mitchell, BSc, FFARCS, and Naina Hindocha

Key Words: GASTROINTESTINAL TRACT, ESOPHAGUS—gastroesophageal sphincter. SURGERY—laparoscopy.

There is controversy regarding the optimal anesthetic technique for laparoscopy. Most authors recommend use of controlled ventilation but, even when spontaneous respiration has been used, tracheal intubation is usually advocated because of the potential danger of acid aspiration (1).

Although it has been assumed that the combination of Trendelenburg position and pneumoperitoneum must predispose to passive regurgitation (2), the incidence appears to be low (3), and there has been no report of the effect of this increased intra-abdominal pressure on the lower esophageal sphincter (LOS).

The lower esophageal sphincter, detected by intraluminal manometry, represents the major barrier to gastroesophageal reflux (4). The overall resistance to gastroesophageal reflux can be expressed quantitatively by calculation of the barrier pressure (BrP), that is, the pressure differential between the LOS and the stomach (BrP = lower esophageal sphincter pressure (LOSP) minus gastric pressure [GP]). The functional integrity of this physiologic sphincter can be affected by many drugs used in anesthetic practice and consequently any drug which decreases LOS tone (e.g., atropine) may be expected to increase the possibility of regurgitation, whereas drugs that increase LOS tone (e.g., metoclopramide) may be expected to reduce this risk.

The lower esophageal sphincter is capable of a rapid adaptive response to increases in intragastric pressure, as has been previously reported during the fasciculations seen after the administration of succinylcholine (5), so that barrier pressure is maintained. We now report the effects of peritoneal insufflation in gynecologic patients undergoing laparoscopy to investigate whether such an adaptive response occurs secondary to the increase in intragastric pressure.

Methods

Six healthy female patients undergoing laparoscopy gave informed consent to participate in the study, which was approved by the District Ethical Committee. None had histories of gastrointestinal disease or were receiving any drug therapy.

Each patient received a standardized anesthetic technique. Premedication consisted of diazepam 10 mg orally preoperatively. Thiopental 4 mg/kg was used to induce anesthesia and tracheal intubation was facilitated by the administration of alcuronium 0.3 mg/kg. Anesthesia was maintained with 70% nitrous oxide and 0–1% enflurane in oxygen with 10 mg morphine for analgesia.

The esophageal manometry tube (Gaeltec Ltd, Isle of Skye, Scotland) was connected via a preamplifier to a multichannel chart recorder. Essentially the manometry tube consists of a fine silastic orogastric tube (3-mm diameter) into which is embedded a subminiature strain gauge pressure transducer 15 cm from the distal tip. Before each investigation, the whole system was calibrated in a water column (scale 0–50 cm H_2O) and this maneuver was repeated at the end of each study to confirm the absence of significant calibration or zero baseline drift. When a stable anesthetic state had been achieved, the esophageal manometry tube was passed through the patient's mouth until the pressure transducer was in the stomach. Measurements of GP, LOSP, and esophageal pressure (OP) were made at end expiration by a "pull through" maneuver previously described (4,6). Essentially, the transducer is slowly withdrawn from the esophagus over a period of 20–30 seconds, enabling sequential recordings of the pressures to be obtained.

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Address correspondence to Dr. Jones, Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW, England

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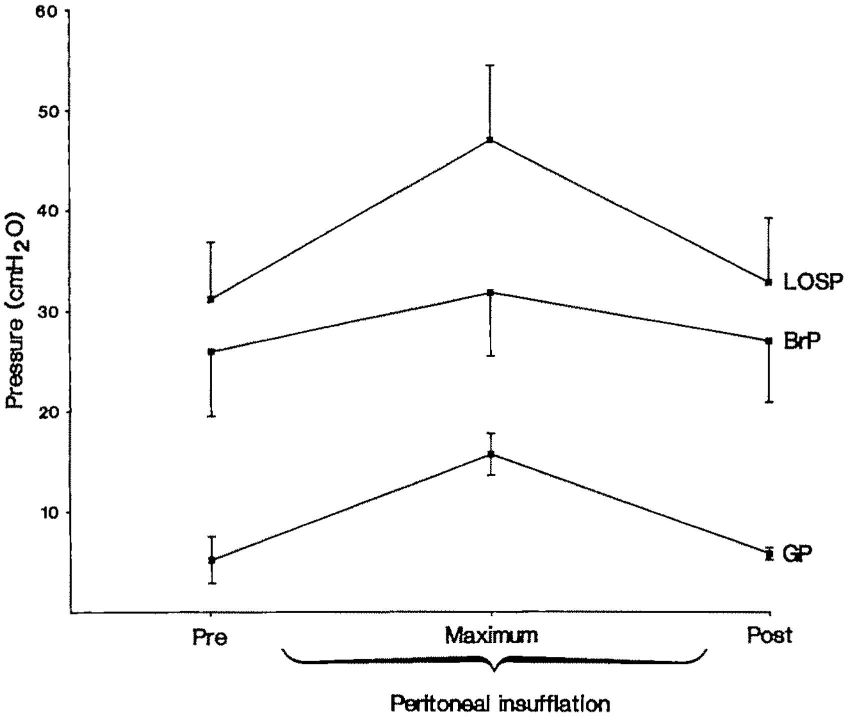

Figure 1. Measurement of lower esophageal sphincter pressure (LOSP), barrier pressure (BrP), and gastric pressure (GP) (mean ± SEM) before (pre), during, and after (post) peritoneal insufflation ($n = 6$).

Measurements of LOSP, GP, and OP were made before, during, and after peritoneal insufflation with carbon dioxide to a maximum intraperitoneal pressure of 30 cm H_2O. Recordings were made with the patient in the lithotomy position in a 10–15° head-down tilt.

Results

Intragastric pressure increased from an initial 5.2 ± 2.3 cm H_2O (mean ± SEM) to 15.7 ± 2.1 cm H_2O ($P < 0.01$) during peritoneal insufflation (Fig. 1). There was an accompanying increase in LOSP from an initial 31.2 ± 5.6 cm H_2O to 47.0 ± 7.4 cm H_2O ($P < 0.05$) at maximal intraperitoneal pressure. Resultant BrP was maintained or increased in five of the six patients. Once the peritoneal cavity had been emptied of gas on completion of surgery, GP decreased to 5.8 ± 0.6 cm H_2O, with a corresponding LOSP of 32.8 ± 6.4 cm H_2O, values similar to those before peritoneal insufflation.

Discussion

Although laparoscopy has become a routine procedure for sterilization or diagnostic purposes, the optimal anesthetic technique remains debatable. Most authorities recommend tracheal intubation with controlled ventilation to reduce the potential dangers of acid aspiration, hypoventilation, and cardiac arrhythmias. However, Scott (7) has questioned the necessity of tracheal intubation with its possible complications, and also pointed out that although arrhythmias are common during spontaneous ventilation with nitrous oxide/halothane anesthesia for this procedure, none appear to be of a serious nature (8).

Accepted clinical teaching in anesthesia is that the combination of the Trendelenburg position and abdominal distension must predispose to passive regurgitation. To our knowledge only one study has investigated the frequency of regurgitation during laparoscopy (3) and it found an incidence of <2%. This particular study can be criticised in that all patients were given atropine 0.6 mg IV at induction, a drug known to markedly reduce LOS tone (9).

Lind et al. (10) found that increasing intra-abdominal pressure resulted in an adaptive increase in LOS pressure. Further evidence of this acute adaptive response was provided by Smith et al. (5), who showed that the increased intragastric pressure produced by succinylcholine as a consequence of muscle fasciculations caused a corresponding greater increase in LOS pressure with a net overall increase in barrier pressure. Our present observations confirm the presence of such an adaptive response of the lower esophageal sphincter in response to peritoneal insufflation during laparoscopy.

Although discussions will persist as to whether patients should undergo controlled ventilation or be allowed to breathe spontaneously, with or without tracheal intubation, we conclude that the raised intraperitoneal pressure does not necessarily increase the likelihood of regurgitation, and should, perhaps, not be a determining factor in the choice of anesthetic technique most appropriate for an individual patient. However, other considerations such as hypoventilation and cardiac arrhythmias dictate that most anesthetists will continue to advocate tracheal intubation.

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Effect of Epidural and Intrathecal Morphine on the Length of Hospital Stay After Cesarean Section

Sally J. Stenkamp, MD, Thomas R. Easterling, MD, and H. S. Chadwick, MD

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL AND SPINAL: opioids. PAIN, postoperative. ANESTHESIA—obstetric.

The ability of epidural or intrathecal (subarachnoid) morphine to provide prolonged analgesia after cesarean section and thus reduce the need for parenteral narcotics is well established (1–3). In addition, patients given epidural morphine after cesarean section become ambulatory 6 hours earlier than those given intravenous morphine for relief of pain (4). Epidural opiate analgesia can reduce morbidity in high risk surgical patients and thereby improve outcome (5,7).

Because regional (i.e., epidural or intrathecal) narcotics provide excellent postoperative pain relief, earlier ambulation, and reduced morbidity, we hypothesized that this might be reflected in a shorter postoperative hospital stay. This study was designed to evaluate the effect of epidural and intrathecal morphine analgesia on the length of hospital stay after elective repeat cesarean section.

Methods

After receiving Human Subjects Review Committee approval, a retrospective review was made of the charts of 219 women who underwent repeat cesarean section at our institution with either epidural or spinal anesthesia. Patients having primary cesarean sections, diabetes requiring insulin therapy, hypertension requiring magnesium sulfate or antihypertensive therapy, cardiac disease, Rh disease, seizure disorder, respiratory disease requiring drug treatment, multiple gestation, placenta previa, abruption, or premature delivery were excluded. In addition patients who left the hospital against medical advice or who had prolonged stays for social reasons were excluded.

The 219 women were classified into two groups, the control group and the study group. The control group (n = 103) comprised women who underwent repeat cesarean section between September 1984 and the end of 1985 with either spinal or epidural anesthesia and who received systemic narcotics for postoperative analgesia. The study group (n = 113) comprised women who underwent repeat cesarean delivery between October 1985 and August 1987 with a regional anesthetic and who received either spinal or epidural morphine for postoperative pain relief. Epidural morphine was given once in a dose of 3 to 5 mg immediately after delivery. The subarachnoid dose was 0.3 to 0.5 mg given at the time that spinal anesthesia was administered. The mean epidural morphine dose was 4.2 ± 0.5 mg and the mean subarachnoid morphine dose was 0.4 ± 0.1 mg. We began using regional morphine for analgesia after cesarean section during October 1985 and by December 1985 almost all patients undergoing cesarean delivery with regional anesthesia at the University Hospital had intrathecal or epidural morphine. For this reason the control group is by necessity a predominantly historical one.

Maternal age, gravidity, parity, insurance coverage, total length of hospital stay in hours, dose of epidural or intrathecal morphine, total dose of parenteral narcotics, and the presence of endometritis were abstracted from hospital charts. Length of hospital stay was defined as the difference between the anesthesiologist's recorded time of the start of the operation and the time of discharge. If the patient was discharged before 10:00 AM, discharge time was arbitrarily assigned as 8:00 AM to control for time discrepancies associated with rounding schedules. If the patient was discharged after 10:00 AM, the time of the doctor's discharge order was used. If the time was not recorded, the time that the nurse signed off the order was taken as the discharge time. If the time of discharge was conditional, the actual time the patient

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Address correspondence to Dr. Chadwick, Department of Anesthesiology, University of Washington, Seattle, WA 98195.

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Table 1. Demographic and Descriptive Patient Variables

	Epidural		Spinal	
	Control (n = 38)	Study (n = 51)	Control (n = 68)	Study (n = 62)
Age (yrs)	26 ± 4	26 ± 6	27 ± 6	26 ± 4
Mean gestational age (weeks)	39 ± 1	39 ± 1	39 ± 1	39 ± 1
Mean pregnant weight (kg)	82 ± 16	82 ± 20	81 ± 18	83 ± 19
(n for weight only)	(n = 31)	(n = 45)	(n = 61)	(n = 55)
Gravidity	3.4 ± 1.6	3.6 ± 1.7	3.8 ± 1.6	3.6 ± 1.5
Parity	1.3 ± 1.6	1.7 ± 1.0	1.9 ± 1.1	1.5 ± 0.7
Prior c-sections	1.2 ± 0.5	1.4 ± 0.6	1.5 ± 0.6	1.3 ± 0.6
Medical insurance	11 (29%)	17 (33%)	13 (19%)	14 (23%)
Bilateral tubal ligations	8 (21%)	24 (47%)*	34 (50%)	16 (26%)†
Postpartum endometritis	5 (13%)	5 (10%)	5 (13%)	3 (5%)
Prophylactic antibiotics	21 (55%)	20 (39%)	24 (35%)	25 (40%)

*P = 0.02 for epidural study group compared with epidural control group.
†P = 0.01 for spinal study group compared with spinal control group.

left the hospital was assigned as the discharge time. Morphine equivalents were used in calculating total parenteral narcotics administered (8,9)

Statistical analysis was by χ^2 test, unpaired Student's t-tests, and correlation coefficient as appropriate. Unless otherwise indicated, values are given as means ± SD.

Table 2. Amounts of IV or IM Narcotics Required*

	Control	Study	P Value
Spinal anesthesia	92 ± 88 (n = 68)	26 ± 52 (n = 62)	<0.001
Epidural anesthesia	87 ± 50 (n = 38)	28 ± 44 (n = 51)	<0.001
All	91 ± 77 (n = 106)	27 ± 49 (n = 113)	<0.001

*Calculated as mg morphine equivalents.

Table 3. Length of Hospital Stay (hrs)

	Control	Study	P Value
Spinal anesthesia	102 ± 26 (n = 68)	93 ± 21 (n = 62)	0.01
Epidural anesthesia	104 ± 25 (n = 38)	101 ± 28 (n = 51)	0.33
All	103 ± 26 (n = 106)	97 ± 25 (n = 113)	0.04

Results

Demographic and descriptive variables of the 113 women in the study group and the 106 women in the control group are summarized in Table 1. The groups were similar with respect to age, gravidity, parity, mean gestational age, prior number of cesarean sections, mean weight at time of delivery, medical insurance coverage, incidence of endometritis, and use of prophylactic antibiotics. Only the incidence of tubal ligations was significantly different. In the women given epidural anesthesia, 21% of the control patients had tubal ligations compared with 47% of patients in the study group (P = 0.02). In patients given spinal anesthesia, 50% of the control group had tubal ligations compared with 26% of the study group (P = 0.01). As expected, patients in the study group required substantially less supplemental IV or IM narcotic analgesia (Table 2).

As shown in Table 3, the mean length of hospital stay of the study group was 97 hours, while the mean stay of the control group was 103 hours (P = 0.04). The difference between groups was attributable primarily to the difference in length of hospital stay between patients who had spinal anesthesia with (study patients) or without (control patients) intrathecal morphine for the relief of postoperative pain (P = 0.01). The epidural morphine (study patients) did not have a significantly shorter stay compared with their control group (P = 0.33).

Because the incidence of tubal ligations was different in the spinal and epidural subgroups, length of stay was determined for this variable. The mean length of hospital stay for women undergoing concurrent tubal ligations was 100 ± 24 hours (n = 82) and the mean stay for those not having tubal ligations was 100 ± 26 hours (n = 137).

To assess if a trend toward earlier discharge during the study period confounded the results, length of hospital stay was plotted against date of entry into the study. Because women with postpartum endometritis have longer hospital stays, they were excluded from this analysis to decrease variability in the data and to increase the probability of finding a trend. The correlation coefficient for length of hospital stay versus date of cesarean section for all subjects is −0.181. The correlation coefficient for the control group is −0.188 and for the study group, −0.150.

Discussion

In confirmation of findings by previous investigators, both the spinal and epidural study groups needed significantly less supplemental narcotic postoperatively than did the control group. In addition, this study found significantly shorter hospital stays for women who received regional morphine at the time of cesarean section. The shorter hospital stay in the study group was the result of a marked difference in those given morphine intrathecally. Those who received morphine epidurally were not significantly different from controls. This finding was unexpected.

The finding of a shorter hospital stay in the intrathecal group could be related to better or longer postoperative pain relief compared with that of the group receiving epidural morphine. Better pain relief might result in earlier ambulation (4), earlier return of gastrointestinal function (5) and/or a lower incidence of pulmonary complications (5–7). Although patients in the intrathecal and epidural study groups received nearly equivalent dosages of supplemental IV or IM narcotics (as calculated in morphine equivalents), a previous study in this patient population showed that intrathecal morphine provided a significantly longer duration of analgesia compared with epidural morphine (10).

An alternative hypothesis is that the intrathecal morphine group may have had fewer problems with postoperative ileus than did the epidural morphine group. The mean dose of supplemental IV or IM narcotics was similar in the intrathecal and epidural study groups, although the total amount of narcotic administered was greater in the epidural study group (32 mg) than in the intrathecal study group (26 mg). This difference is primarily because of the greater amount of morphine given epidurally. One might speculate that this difference in total morphine requirement might result in less impairment of bowel motility and therefore shorter hospital stays in the intrathecal group. It seems unlikely, however, that this small difference would have a significant effect in view of the similar length of stay, despite the large difference in total morphine dose, seen in the epidural control and study populations.

The study and control groups were similar with respect to all demographic and descriptive variables except for the numbers of women within the spinal and epidural subsets who underwent concomitant tubal ligations. If tubal ligation lengthened hospital stay, the differences in the frequency of this procedure might explain the differences in hospital stay. Tubal ligation was, however, not associated with a longer hospital stay and thus does not explain the observed differences. The finding that the study and control groups had similar rates of postpartum endometritis is important because women with endometritis have longer hospital stays. When the data were analyzed excluding cases with endometritis, the results were unchanged.

Given the predominantly historical control group, any trend toward earlier hospital discharges during the period of this study would confound the results. We addressed this issue by analyzing the length of hospital stay in relation to the date of cesarean delivery. The small values of the correlation coefficients seen when the length of hospital stay is plotted against date of entry into the study makes it impossible to determine a trend toward decreasing length of stay in either the control or study groups. Further, if a trend toward earlier discharge during the study period were to explain the difference in length of hospital stay, a similar difference should be seen in the epidural subset as was observed in the intrathecal subset.

The shorter hospital stay in the study group (6 hrs) and especially in the intrathecal subgroup (9 hrs), although apparently small, is an important finding. It implies that even in the low risk cesarean population, which we studied, there may be a more rapid recovery or lesser morbidity, resulting in shorter hospital stay and reduced financial expenditure for the patients.

Although we excluded many categories of patients to avoid confounding variables, it is possible that the study and control groups are different with respect to variables that we did not evaluate and that our results are confounded by these differences. Because patients were not randomized into spinal and epidural subgroups, the possibility that a selection bias is operating cannot be dismissed. A prospective study with women randomized to spinal and epidural groups and randomized to receive either regional morphine or systemic narcotics is needed to confirm the findings of this study.

In conclusion, a retrospective chart review was employed to evaluate the effect of intrathecal and epidural morphine analgesia on the length of hospital stay in women having repeat cesarean deliveries. Women who were given neuraxial morphine for postoperative pain relief had a shorter length of hospital stay than did those given IV and IM narcotics ($P = 0.04$). An unexpected finding was that the shorter hospital stay in the study group was the result of a markedly shorter stay in those who were given morphine intrathecally ($P = 0.01$). Those who were given morphine epidurally were not significantly different from their controls ($P = 0.33$).

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Cessation of Shivering and Hypothermia Associated with Epidural Sufentanil

Mark D. Johnson, MD, Ferne B. Sevarino, MD, and Mark J. Lema, PhD, MD

Key Words: COMPLICATIONS—shivering. ANESTHESIA—obstetrical. ANESTHETIC TECHNIQUES—epidural.

Shivering is a common peripartum problem and its incidence is further increased when regional anesthesia is used. Measures to prevent heat loss often do not prevent shivering. We observed the cessation of shivering and a decrease in body temperature in a patient given sufentanil epidurally after undergoing a cesarean delivery with epidural lidocaine anesthesia.

Case Report

A 22-year-old female, ASA physical status I, G_1P_0 presented at 40 weeks' gestation with a breech presentation for a primary elective cesarean delivery. She was given 1500 ml warm (37°C) Ringer's lactate solution IV and, while being given oxygen by mask at 5 L/min, epidural anesthesia was induced at the L2–3 interspace using the loss-of-resistance technique. After a negative test dose of 3 ml of 2% lidocaine with 1/200,000 epinephrine, a T3 level of sensory anesthesia was produced using 3-ml incremental doses of 2% lidocaine with 1/200,000 epinephrine to a total dose of 24 ml. Bilateral sacral lumbar motor block was also present. No shivering was noted at this time. She was then taken to the operating room where she had an uneventful cesarean delivery of a male infant. Blood loss was estimated to be 1200 ml. Total time in the operating room was 72 minutes. The operating room temperature was 27°C. While in the operating room, her legs, arms, and shoulders were wrapped in warm blankets and she received 3000 ml warmed (37°C) Ringer's lactate solution IV. On arrival in the recovery room, her oral temperature was 35°C and she was shivering.

This patient had been enrolled, after informed consent, in a post-cesarean section epidural sufentanil dose-response study approved by the Brigham and Women's Hospital Committee for the Protection of Human Subjects from Research Risks (1). The study protocol dictated that when the patient's epidural local anesthetic sensory block had regressed to the point that she complained of pain (defined as a pain score of greater than 3 on a 0–10 cm visual analogue pain scale [2]), a study medication (a blinded, random selection of 0–100 μg sufentanil in normal saline was injected epidurally). No other medications were given. Within 6 minutes, she was pain-free and her shivering had completely stopped. However, she had onset of nausea and pruritis of the upper chest and neck. No urticaria was detected and her lungs were clear to auscultation. Blood pressure and pulse were stable at 110/65 to 130/80 mm Hg and 80–90 beats/min, respectively. Respiratory rate was 18 breaths/min and oxygen saturation by finger pulse oximetry was 97%. Her oral temperature decreased from 35°C to 33°C over the next 30 minutes despite use of warm blankets, radiant heat, and warmed IV fluids. She did not shiver during this period. She was alert, oriented, and pain-free, but continued to complain of nausea and pruritis. The study code was broken and it was determined that she had received 100 μg of sufentanil diluted in 10 ml of preservative-free normal saline as her study medication. Her symptoms were considered to be secondary to the epidural sufentanil (as opposed to an allergic reaction) and naloxone 0.1 mg was administered IV. Within 5 minutes, the nausea and pruritis resolved and shivering started again. She was discharged from the recovery room 2 hours later with an oral temperature of 37°. Her nausea and pruritis had resolved, and she was still pain-free. She was subsequently monitored for 24 hours and experienced no further complications.

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Address correspondence to Dr. Johnson, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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Discussion

Body temperature regulation is controlled by the thermoregulatory centers of the hypothalamus (3). It is well established that narcotics alter the response of the thermoregulatory center to changes in body temperature in animals (4). Although the mechanism of action is not well established, possible mechanisms include the centrally mediated suppression of shivering thermogenesis or peripheral vasoactive effects resulting in the redistribution of body heat.

Shivering is a commonly reported side effect of regional anesthesia (5). Warming (to 37°C) IV crystalloid solutions used for volume expansion (6) and warming (to 37°C) local anesthetics used for regional anesthesia (7) are not completely effective in preventing shivering. Shivering is often seen in patients in labor who have received no anesthetic or IV fluids. The incidence increases when regional anesthesia is used, and may often be the only complaint in a well managed anesthetic. Parenteral narcotics have been suggested to reduce the incidence of shivering associated with regional anesthesia (8) and with general anesthesia (9).

In the present case, the patient's shivering was an appropriate response to her reduced core temperature. After the administration of 100 μg epidural sufentanil, the cessation of shivering and the onset of nausea and pruritis appeared to be temporarily related. The reduction in temperature was profound despite the use of warm blankets, radiant heat, and warmed IV fluids. After the administration of 0.1 mg IV naloxone, the nausea and pruritis resolved almost immediately but, with the concurrent resumption of shivering and subsequent increase in core temperature, it would seem that the epidural sufentanil also contributed to the development of the hypothermia.

Perhaps epidural sufentanil (or other epidural narcotics) in the proper dose may prove useful in reducing the incidence of shivering related to regional anesthesia. However, because shivering may serve a useful purpose in maintaining core temperature, further studies are needed to determine if the ability of epidural sufentanil to prevent intra- and postoperative shivering is of physiologic benefit.

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Letters to the Editor

Negative Inotropic Effects of Esmolol

To the Editor:

In a recent paper (1), Sidi and Davis report that infusion of esmolol 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ before and during occlusion of the left anterior descending coronary artery (LAD) decreases lactate production and hemodynamic impairment caused by myocardial ischemia in anesthetized dogs. Unfortunately, these authors chose not to compare their control (no esmolol) and treatment (esmolol) groups. Inspection of Table 1 in their paper reveals that there were striking differences in hemodynamics prior to occlusion of the LAD between animals in the control group and animals receiving esmolol: stroke volume index, 42.6 ± 4.7 vs. 25.2 ± 3.3 $ml \cdot beats^{-1} \cdot m^{-2}$; left ventricular stroke work index, 54.7 ± 10.7 vs. 29.4 ± 4.0 $g \cdot m^{-2} \cdot beats^{-1}$; left ventricular dP/dt, 1886 ± 165 vs. 1688 ± 219 $mm\ Hg \cdot min^{-1}$; systemic vascular resistance, 2584 ± 289 vs. 4906 ± 830 $dynes \cdot sec \cdot cm^{-5}$; pulmonary vascular resistance, 307 ± 39 vs. 654 ± 89 $dynes \cdot sec \cdot cm^{-5}$ (mean ± SEM, control group vs. treatment group, period 1 data). These data were not statistically compared, but it would appear that esmolol caused significant myocardial depression prior to the ischemic insult. Admittedly, this interpretation is complicated by the way in which the data are presented, in that some of animals from which these mean esmolol data were derived underwent an LAD occlusion an hour prior to receiving the esmolol. Nevertheless, a likely explanation for the observation of less hemodynamic impairment secondary to LAD occlusion in the esmolol group with respect to baseline than in the control group with respect to baseline is that myocardial function in the animals receiving esmolol was so markedly impaired prior to the LAD occlusion that little additional dysfunction could be induced by the period of ischemia. Thus, the study design and statistical analysis preclude definitive conclusions about the myocardial protective effects of esmolol.

Table 1. Heart Rate (HR) Response to 5.0 μg of Isoproterenol

	Period 1		Period 2	
	Baseline HR (beats/min)	HR Change (beats/min)	Baqseline HR (beats/min)	HR Change (beats/min)
Control (n = 9)	107.7 ± 5.4	72.9 ± 17.7	108.4 ± 15.4	76.1 ± 17.6
Treatment (n = 8)	98.6 ± 9.7	86.8 ± 18.1	95.9 ± 11.8	89.8 ± 33
Esmolol in period 1 (n = 4)	97.8 ± 9.1	83.8 ± 19.1	94 ± 9.9	81 ± 40.1
Esmolol in period 2 (n = 4)	99.5 ± 10.2	89.8 ± 18.2	97.8 ± 13	98.5 ± 21.7

Values are means ± S.D. Baseline HR, HR observed prior to isoproterenol (5.0 μg) infusion; HR change, peak increase of HR observed following isoproterenol infusion.

I am also intrigued by several other aspects of this paper. According to the description of the methods, isoproterenol challenges were administered to each animal, but no data are reported or discussed. Likewise, the authors state in the final paragraph that heart rate "was controlled artificially," but there is no mention of a pacing protocol in the Methods. Finally, the paper by de Bruijn, Croughwell, and Reves (2) is cited to support the assertion that esmolol has increasingly negative inotropic effects in dosages greater than 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$. This is clearly inappropriate, since de Bruijn and his colleagues did not examine or discuss this issue.

James R. Jacobs, PhD
Medical Research Associate
Duke University Medical Center
Durham, NC

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In Response:

We welcome the opportunity to respond to the letter from Dr. Jacobs, which expressed some concerns regarding our recent study of the effects of the β-adrenergic receptor antagonist, esmolol, in a canine model of acute cardiac ischemia produced by transitory left anterior descending coronary artery (LAD) occlusion (1). Dr. Jacobs has raised several important points regarding that study which deserve a detailed response.

First, we maintain that, in fact, we did compare esmolol treatment with no esmolol treatment. Our study design involved two primary elements; one was the time-related sequential LAD occlusion (15 minutes) separated by a

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60-minute reperfusion interval, and the other was the randomized assignment of esmolol treatment to either the first or second occlusion period. The "control" group to which Dr. Jacobs refers received no esmolol during either occlusion period in order to evaluate *only* the time-related effects of the sequential occlusion design of the study (i.e., findings in the second occlusion period as compared with those in the first occlusion period). As documented by the data reported in our study, the responses to the first LAD occlusion were essentially the same as those to the second LAD occlusion in the animals that received no esmolol during either occlusion period. The second group, the "treatment" group, received esmolol, by randomized assignment, during only one of the two occlusion periods. For purposes of data analysis, results in this group, only, were collated by treatment rather than by time so that esmolol treatment could be compared with no esmolol treatment. Because the data reported for the control group were sequentially obtained, while those for the treatment group were arranged according to esmolol treatment or no esmolol treatment without regard to the time sequence (i.e., occlusion period 1 or 2), a time-wise comparison of the control and treatment groups is not justified. Moreover, the fact that there were only minor differences between periods 1 and 2 in the control group strengthens, rather than weakens, our conclusions regarding the impact of esmolol treatment.

It would be surprising if β-adrenergic receptor antagonism did not depress myocardial function to some degree. However, we disagree that the magnitude of any such depression was sufficient, such that myocardial function was "so markedly impaired prior to the LAD occlusion that little additional dysfunction could be induced by the period of occlusion." In fact, the data show that in the treatment group, the period 1 before occlusion values (i.e., with esmolol "on board," but with the LAD open) are nearly identical to the corresponding period 2 (i.e., no esmolol) values for all hemodynamic and metabolic measurements. From that very similar baseline, deleterious changes in hemodynamic and metabolic variables were more frequently seen in period 2 (no esmolol) than in period 1 (with esmolol).

The isoproterenol "challenge" was not used to document the degree of beta-adrenergic receptor blockade; that procedure requires determination of a heart rate dose-response curve to isoproterenol during steady-state β-blockade, or vice versa. We used a fixed intravenous dose of isoproterenol (5 μg) in order to show that the beta antagonism of esmolol when it was administered during the first occlusion period had completely disappeared by the time of the second occlusion period. For the sake of uniformity this dose of isoproterenol was administered prior to both occlusion periods in each animal in both study groups. Dr. Jacobs correctly points out that data from this procedure were not contained in our report. Simply stated, the response to isoproterenol was no different in period 1 from that in period 2 in the control group. Also, in the treatment group, as a whole, there was no difference comparing the response prior to the period without esmolol to that prior to the period with esmolol. Furthermore, a breakdown of the treatment group into the two subgroups (esmolol in period 1 or esmolol in period 2) shows no difference in the response to isoproterenol based upon the time period of observation relative to esmolol treatment. The numeric data are shown in Table 1. These data show that: 1) there was no time-related change in the response of heart rate to the isoproterenol challenge (control group) and 2) there was no significant influence of esmolol administered in period 1 on the response of heart rate to the isoproterenol challenge administered prior to period 2.

Regarding our pacing protocol, the animals were paced using a right atrial bipolar epicardial electrode system and a standard laboratory stimulator (Grass model #SD9) set to deliver a fixed rate impulse of 5 msec duration and 5 v. Pacing was begun after sinus node ablation produced by formalin injection at the junction of the superior vena cava and the right atrium. The pacemaker was used to prevent esmolol-related reduction of heart rate. However, if heart rate increased during LAD occlusion, relative to the before occlusion value, no intervention was made.

Finally, Dr. Jacobs is correct that the work of Bruijn et al. (2) was incorrectly cited in conjunction with our statement that higher doses of esmolol may cause increasing myocardial depression because, in that study, the effect of higher doses on hemodynamic function was not examined. The work of Girard et al. (3) does show a greater increase of pulmonary capillary wedge pressure and a greater decrease of stroke index when the change from baseline with a 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ esmolol infusion is compared with that of 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion in anesthetized patients. Thus, our statement that "higher doses of esmolol (>200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) have increasingly negative inotropic effects" appears to be true, although an incorrect reference was inadvertently cited to substantiate the statement. We thank Dr. Jacobs for his thoughtful comments regarding our work and hope that the additional information presented here clarifies the issues raised by his letter.

Richard F. Davis, MD
Department of Anesthesiology
University of Florida College of Medicine
Gainesville, Florida

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Glossal Pulse Oximetry

To the Editor:

Pulse oximetry is now generally recognized as part of routine monitoring in all patients having general anesthe-

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Book Reviews

The Care of Strangers, The Rise of America's Hospital System

C. E. Rosenberg. New York: Basic Books 1987, 437 pp, $22.95.

"The hospital has become so central to medical care that it is difficult to reconstruct the world in which it played only a marginal role." However historian Rosenberg describes a time during which hospitals were not only not central, but to be shunned; as he traces the evolution of hospitals in the 19th and early 20th centuries from a repository for the destitute and friendless to the medical centers which now exist. Because of this early image, "until the 1920s surgery was often performed in private homes, and babies were in many cases still delivered in the mother's bedroom, whether attended by a family physician or midwife."

Much of this evolution took place between 1870 and 1920. Although this coincides with the time during which Florence Nightingale's impact on the professionalism of nursing was most dramatic, other forces also played a role. In particular, the hospital had become central to medical education and "been clothed with a legitimate aura of science and almost boundless social expectation." Rosenberg suggests that a new group of specialties—clinical pathology, anesthesiology, and radiology—grew directly out of hospital needs and largely in hospital context. For example, the administration of anesthesia was originally part of house officers' every day duties (to spare hospital budgets and as a preparation for careers in which they would be administering anesthesia to private patients and those of their friends). The 14 chapters of this book present a picture which is both chronologic (1800–1850 and 1850–1920) and topical (e.g. science, education, paying patients) in an extremely well-documented manner. Archives of some of America's most famous hospitals as well as others less well-known in addition to such well-recognized information sources as the *Boston Medical and Surgical Journal* and JAMA are cited to support statements. This book cannot be read lightly. To appreciate fully the history of our hospital based system of medicine one must read the many notes which accompany each chapter.

For this reviewer, the last chapter (The Past and the Present) hit an especially responsive chord. In this era of cost containment, when physicians have become "providers" and patients "consumers" in the "health care industry," the emphasis on minimizing inpatient care sounds like a throwback to another time when patients would literally rather be dead than hospitalized. With respect to cost containment, the decrease in average length of stay from more than 42 to fewer than 21 days between 1870 and 1900 makes any further decrease in the 1980s seem minuscule. What will be the outcome of this cost containment emphasis? In the final sentences of the book Rosenberg concludes that there is ". . . little prospects of hospitals in general becoming monolithic cost minimizers and profit maximizers. Social expectations and well established interest are both inconsistent in such a state of things. We will support research and education, we will feel uncomfortable if the medical system does not provide a plausible (if not exactly equal) level of care to the poor and socially isolated. Health care policy will continue to reflect a special character of our attitudes towards sickness and society."

Norig Ellison, MD
Professor of Anesthesia
Acting Chairman
Department of Anesthesiology
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104

The Pharmacologic Approach to the Critically Ill Patient

B. Chernow, ed. Baltimore: Williams and Wilkins, 1988, 975 pp, $116.50.

Advancements in critical care medicine include mechanical ventilatory support, parenteral nutrition and cardiopulmonary monitoring, but no aspect has changed more rapidly or offerred more to patient care than the progress in drug therapy. With this focal point, Dr. Chernow has vastly improved without vastly expanding this multiauthored text since the 1983 edition.

The first section covers "Clinical Pharmacology." The obligatory "Pharmacokinetics" (for beginners) and "Drug Interactions" chapters are followed by excellent discussions of drug management when various organs fail. An exhaustive table of dose adjustments for liver failure is particularly helpful and well-referenced. "Cardiovascular Adrenoreceptors" is not the expected rehash of basic physiology, but a clear, scholarly explanation of receptor, endogenous effector, and drug interrelationships.

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"Resuscitation Pharmacology" has been revised to the new ACLS standards and includes an unusually lucid discussion of the bicarbonate problem. Since the crystalloid-colloid controversy has cooled in the last five years, the new chapter flows from distribution of body water, through the controversial fluid studies, to an empiric approach to fluid resuscitation without the bias noted in the first edition.

Dr. Chernow's bias to endocrine and affection for hot research topics is relfected in the distribution of chapters. Steroids, calcium, thyroid hormones, endogenous opiates, and plasma fibronectin are given a high profile. Antimicrobials, the most frequently used and most commonly abused drugs, are given cursory coverage.

This is a clinical work, and most authors used commendable restraint regarding the depth of pathophysiology appropriate for their readers. Occassional digressions such as diet therapy and oral medications in "Antihypertensive Therapy" must be forgiven for the lack of relevance to ICU care when the remainder of the chapter is pertainent, updated and readable. Giving equal consideration to older drugs makes this reference book appropriate for trainees as well as practitioners of critical care. However, only those groups will find this a practical resource. Others should devote the price and shelf space to a standard pharmacology text or a collection oriented to their own speciality.

Joanne L. Floyd, MD
Director, Intensive Care and Respiratory Care
Assistant Professor, Anesthesiology and Internal Medicine
Albert Einstein College of Medicine
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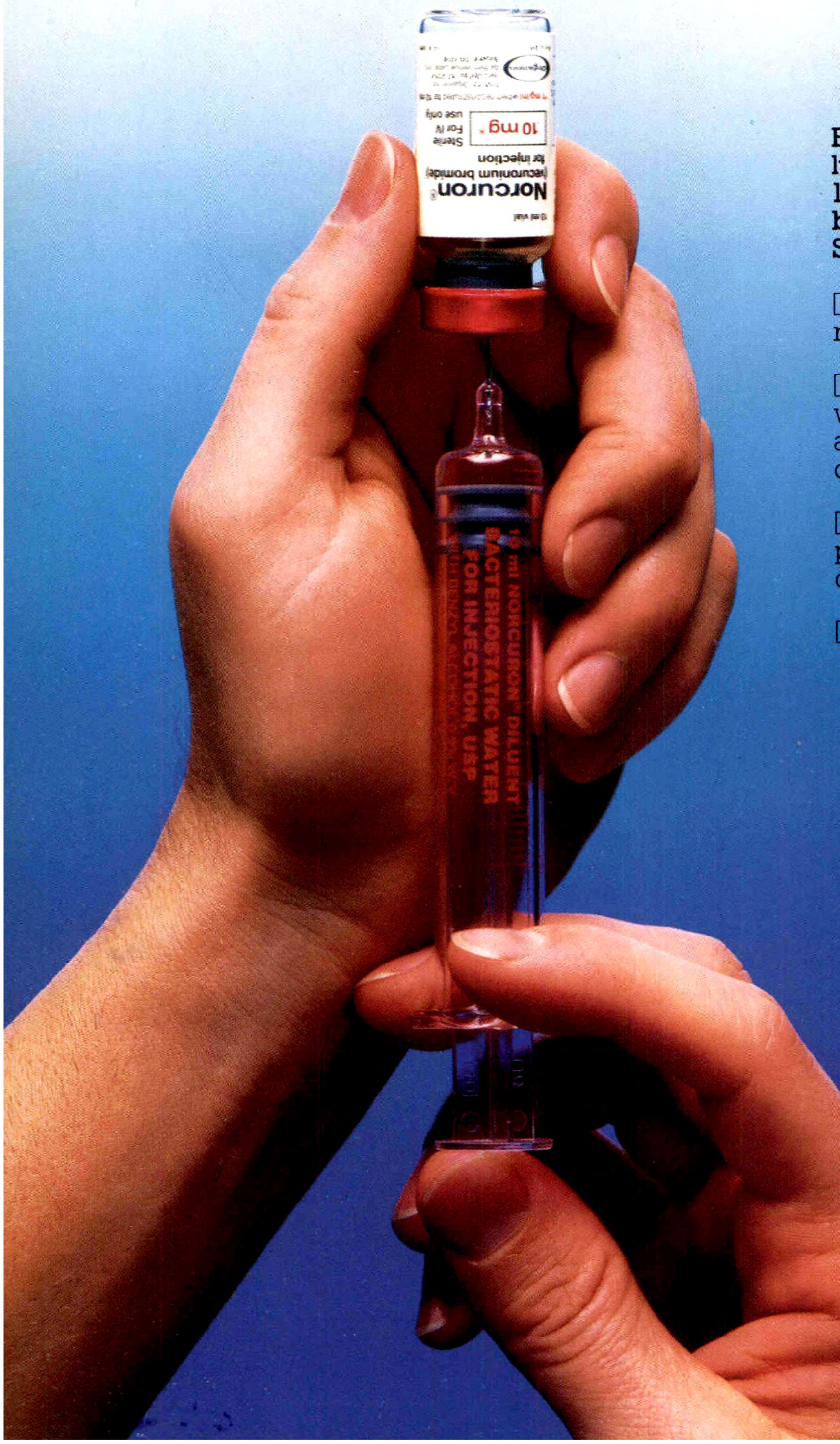

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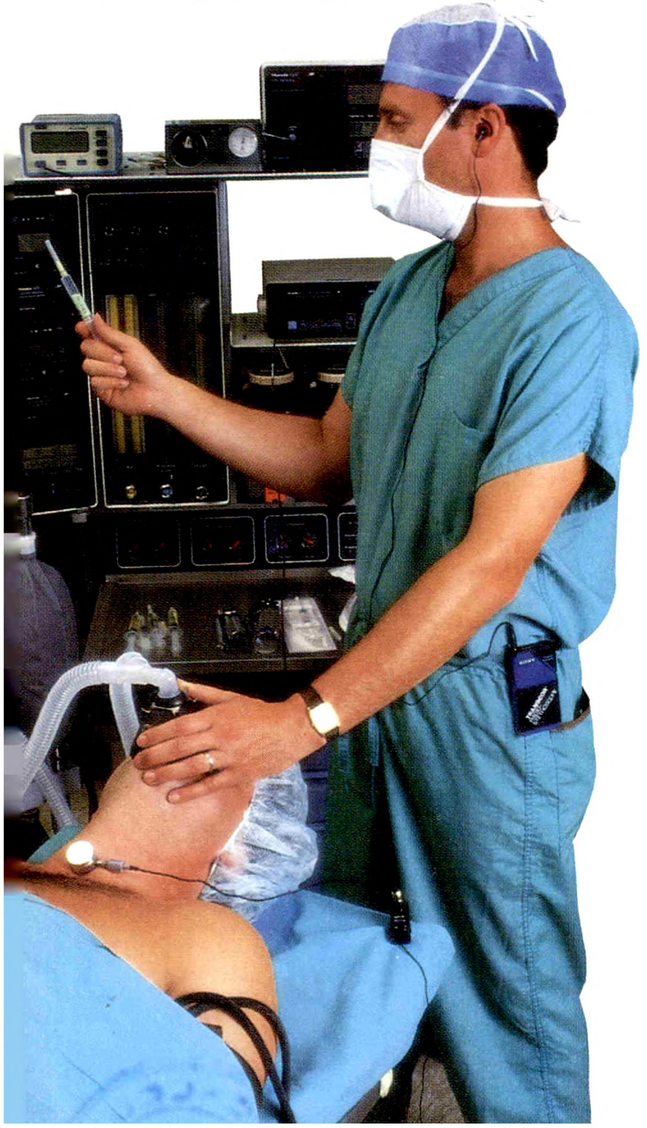

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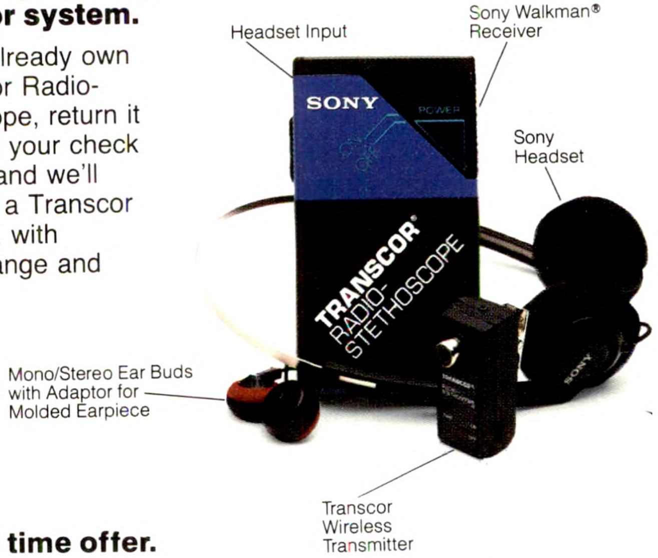
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Quantitative Relationships Between Plasma Beta-Endorphin Immunoactivity and Hemodynamic Performance in Preoperative Cardiac Surgical Patients

Daniel B. Carr, MD, C. G. Athanasiadis, MD, C. T. Skourtis, MD, Scott M. Fishman, BS, Nabil R. Fahmy, MD, and Demetrios G. Lappas, MD

CARR DB, ATHANASIADIS CG, SKOURTIS CT, FISHMAN SM, FAHMY NR, LAPPAS DG. Quantitative relationships between plasma beta-endorphin immunoactivity and hemodynamic performance in preoperative cardiac surgical patients. Anesth Analg 1989;68:77–82.

To quantitate the importance of cardiac dysfunction as a stimulus for plasma immunoactive beta-endorphin (iBE) secretion, we measured iBE and hemodynamic indices in 65 patients prior to anesthetic induction for coronary artery bypass grafting or valve replacement. Linear regression analysis for the group as a whole showed significant correlations between iBE and stroke index (SI), pulmonary artery wedge pressure (PCW), and right atrial pressure (RAP), but not mean arterial pressure (MAP). Two patient subgroups were identified ($P < 0.001$ by F-test): those with low SI and high iBE, or those with high SI and low iBE (cutoffs at 40 ml/m^2 and 35 pg/ml, respectively). Correlations between hemodynamics and iBE were always stronger within the low-SI than the high-SI subgroups. These correlations were greater for patients with coronary artery than with valvular heart disease. Cardiac output (CO) and cardiac index (CI) correlated with iBE in valve-replacement and coronary-grafting groups. These findings were not an artifact of impaired iBE clearance due to renal dysfunction. Our results quantitate the importance of hemodynamic dysfunction for iBE secretion, and indicate that this relationship is particularly strong when stroke index declines below 40 ml/m^2.

Key Words: POLYPEPTIDES—endorphins. ANESTHESIA—Cardiovascular.

The pituitary-adrenal axis is activated by many (1), though not all (2), threatening environmental stimuli. Acute circulatory shock is a potent stimulus to adrenal steroid secretion through a cascade including corticotropin-releasing factor (CRF), vasopressin (AVP), and other mediators which trigger adenocorticotropic hormone (ACTH) release (3,4). Recently, monokines have been found to have CRF activity (5), implying that ACTH release resulting from hypotension of different etiologies may occur through distinct mechanisms, e.g., hypothalamic CRF release during hemorrhage (3) versus interleukin-1 release from monocytes during sepsis (5).

Endogenous opioid peptides are secreted along with other pituitary-adrenal hormones such as ACTH, catecholamines or cortisol (4). In particular, beta-endorphin and ACTH are synthesized from a common precursor molecule and co-secreted (6). Opioids have both central and peripheral cardiovascular actions (7); as with ACTH, it is likely that mechanisms of release and actions of beta-endorphin are distinct during hemodynamic failure of different etiologies (8).

In view of the above, it is desirable that clinical studies of iBE secretion in the presence of hemodynamic pathology employ well-characterized patient populations, free of confounding factors such as hypovolemia and sepsis. Such studies might indicate whether volume overload or ventricular dysfunction are stimuli for iBE secretion, as has recently been found for other biologically active peptides with cardiac actions (see discussion section). Understandably, many clinical studies of endorphins in shock have been based upon responses to naloxone of

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Received from the departments of Anesthesia and Medicine, Massachusetts General Hospital and Harvard Medical School, Boston; Shriners Burns Institute, Boston; and Division of Cardiothoracic Anesthesia, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication July 29, 1988.

Address correspondence and reprints to Dr. Carr: Analgesic Peptide Research Unit; Departments of Anesthesia and Medicine; Massachusetts General Hospital, Fruit Street; Boston, MA 02114.

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patients *in extremis*, in whom multiple factors contribute to their instability. Relatively few studies in this area have exploited the careful preoperative monitoring of cardiac surgical patients (9–12). Yet, of these few, most have examined responses to complex stresses such as surgery or cardiopulmonary bypass (CPB), not relationships between hemodynamics and iBE prior to these interventions. We report correlations between iBE and hemodynamic status determined in cardiac surgical patients prior to induction of anesthesia.

Methods

Sixty-six patients were evaluated prior to induction of anesthesia for coronary bypass grafting (36), valve replacement (26), both procedures combined (3), or thoracic aneurysmectomy (1). Mean age (± SEM) was 60.8 ± 1.2 years (range 27 to 76). All subjects provided informed consent, and were maintained on their individual medical regimens until the day of surgery. All were adequately sedated after premedication with morphine 0.1 mg/kg subcutaneously, scopolamine 0.3 or 0.4 mg intramuscularly, and lorazepam 1 or 2 mg orally. Radial and pulmonary artery catheters were placed using local anesthesia. Electrocardiogram leads II and V_4 were monitored, as were mean arterial (MAP), pulmonary arterial (PAP), pulmonary capillary wedge (PCWP), and right atrial (RAP) pressures. Cardiac output (CO) was measured by thermodilution. Stroke index (SI), stroke volume (SV), systemic and pulmonary vascular resistance (SVR and PVR, respectively) were derived by standard formulae. (Units for each are given in Table 1). One patient undergoing mitral valve replacement, moribund with exceedingly high iBE levels (>3000 pg/ml) and markedly depressed hemodynamic status (e.g., CI = 1.2 $l \cdot min \cdot m^{-2}$, SI = 9.6 ml/m^2), was not included in these analyses.

Arterial plasma was sampled after patients had been moved into the operating room and monitoring lines were in place. Samples were assayed for iBE in duplicate, unextracted aliquots by methods described previously in detail (8,13). Such methods also reflect plasma levels of beta-lipotropin, a precursor (6), and result in normal iBE values of less than 50 pg/ml. Assays of iBE were blinded, i.e., performed on coded specimens. Statistical analyses were performed using standard packages implemented on the CLINFO system of the General Clinical Research Center, Massachusetts General Hospital, using a VAX digital computer.

Table 1. Hemodynamic Indices and Immunoactive Beta-Endorphin in Cardiac Surgical Patients Prior to Induction (all values are mean ± SEM)

	Valve replacement (N = 26)	CABG (N = 36)	Valve + CABG (N = 3)	All (N = 65)
HR	96.0 ± 4.7*	60.3 ± 2.1	70.7 ± 4.4	75.5 ± 3.1
MAP	87.9 ± 3.2	88.5 ± 2.0	87.7 ± 7.2	88.2 ± 1.8
Mean PA	39.6 ± 4.2*	17.4 ± 0.9	30.7 ± 5.8	27.4 ± 2.3
PCW	27.8 ± 2.6*	11.5 ± 0.7	19.3 ± 1.8	18.8 ± 1.5
RAP	12.7 ± 1.4*	5.9 ± 0.4	8.3 ± 2.0	8.9 ± 0.8
CO	3.96 ± 0.2	4.40 ± 0.2	3.83 ± 0.4	4.18 ± 1.1
CI	2.28 ± 0.1	2.34 ± 0.1	2.12 ± 0.2	2.30 ± 0.2
SV	45.3 ± 3.5*	75.6 ± 3.6	55.0 ± 8.3	61.8 ± 3.0
SI	26.1 ± 1.9*	40.2 ± 1.5	30.0 ± 3.2	33.8 ± 1.4
SVR	1634 ± 106	1590 ± 74	1838 ± 485	1620 ± 62
PVR	308 ± 49*	125 ± 12	262 ± 86	207 ± 24
iBE	212 ± 137	36 ± 2.9	67 ± 7.2	107 ± 54

HR, heart rate (/min); MAP, mean arterial blood pressure (mm Hg); mean PA, mean pulmonary arterial pressure (mm Hg); PCW, pulmonary capillary wedge pressure (mm Hg); RAP, right atrial pressure (mm Hg); CO, cardiac output (l/min); CI, cardiac index ($l \cdot min \cdot m^{-2}$); SV, stroke volume (ml); SI, stroke index (ml/m^2); SVR, systemic vascular resistance ($dynes \cdot sec \cdot cm^{-5}$); PVR, pulmonary vascular resistance ($dynes \cdot sec \cdot cm^{-5}$); iBE, immunoactive beta-endorphin (pg/ml).

*P < 0.001 by ANOVA compared with value in CABG group; P = n.s. otherwise.

Results

Mean ± SEM values for hemodynamic indices and iBE are given in Table 1 for all patients, as well as subgroups according to disease. Many values differed between subgroups, suggesting greater circulatory compromise in the patients with valvular heart disease as reflected in higher mean values of heart rate (HR), left- and right-sided cardiac filling pressures, and PVR, and lower mean values of SV and SI in this group. Excellent correlations were present between SI or iBE and many hemodynamic parameters (Table 2A), with the notable exception of MAP. Many of these correlations persisted when the patients were grouped according to diagnosis (Tables 2B and 2C). Only CO (and derived CI) had significant correlations with SI and iBE in both valvular and coronary disease subgroups.

To explore these relationships visually, we plotted iBE against several hemodynamic indices. The results for SI are shown in Figure 1. This graph suggests the presence of two subpopulations having either low SI and high iBE, or high SI and low iBE, regardless of diagnosis. These two subgroups were demarcated by SI = 40 ml/m^2 and iBE = 35 pg/ml ($P < 0.001$ by F-test). Although Figure 1 depicts iBE versus SI, similar findings were present for CO, RAP, and PCW, but not MAP. Indeed, splitting the patient groups according to either SI or iBE (with respective

Table 2A. Correlations Between Stroke Index, Beta-Endorphin Immunoactivity, and Other Measurements in Cardiac Surgical Patients Prior to Induction

	SI		iBE	
	R	*P*	*R*	*P*
iBE	−0.647	<0.001	1.0	—
SI	1.0	—	−0.647	<0.001
HR	−0.795	<0.001	0.587	<0.001
MAP	−0.149	0.244	−0.124	0.355
Mean PA	−0.594	<0.001	0.425	0.001
PCW	−0.675	<0.001	0.702	<0.001
RAP	−0.573	<0.001	0.535	<0.001
CO	0.625	<0.001	−0.455	<0.001
CI	0.516	<0.001	−0.316	0.015
SV	0.956	<0.001	−0.643	<0.001
SVR	−0.449	0.001	0.305	0.018
PVR	−0.532	<0.001	0.720	<0.001
BUN	−0.305	0.019	0.142	0.292
CRE	−0.157	0.234	0.007	0.959

Correlation coefficients ("R" values) were computed by linear regression analysis of untransformed data, i.e., were computed as linear correlations. P values showed no important differences when correlations were based upon log-transformed data. Abbreviations as in Table 1, with the addition of: BUN, blood urea nitrogen (mg/dl); CRE, creatinine (mg/dl).

Table 2B. Correlations Between Stroke Index, Beta-Endorphin Immunoactivity, and Other Measurements in Cardiac Surgical Patients Prior to Induction (valve replacement group only)

	SI		iBE	
	R	*P*	*R*	*P*
iBE	−0.354	0.106	1.0	—
SI	1.0	—	−0.356	0.096
HR	−0.803	<0.001	0.258	0.234
MAP	0.102	0.613	−0.347	0.105
Mean PA	−0.577	0.002	0.317	0.141
PCW	−0.700	<0.001	0.352	0.099
RAP	−0.668	<0.001	0.080	0.718
CO	0.658	<0.001	−0.424	0.044
CI	0.673	<0.001	−0.428	0.041
SV	0.944	<0.001	−0.378	0.075
SVR	−0.336	0.087	0.119	0.599
PVR	−0.466	0.029	−0.331	0.133

Legend as for Table 2A.

Table 2C. Correlations Between Stroke Index, Beta-Endorphin Immunoactivity, and Other Measurements in Cardiac Surgical Patients Prior to Induction (coronary bypass group only)

	SI		iBE	
	R	*P*	*R*	*P*
iBE	−0.697	<0.001	1.0	—
SI	1.0	—	−0.697	<0.001
HR	−0.647	<0.001	0.419	<0.014
MAP	−0.300	0.080	0.231	0.189
Mean PA	−0.260	0.132	0.064	0.719
PCW	−0.303	0.073	0.083	0.634
RAP	0.079	0.647	−0.210	0.227
CO	0.653	<0.001	−0.454	0.006
CI	0.618	<0.001	−0.368	0.029
SV	0.942	<0.001	−0.673	<0.001
SVR	−0.695	<0.001	0.524	0.001
PVR	−0.314	0.066	−0.031	0.861

Legend as for Table 2A.

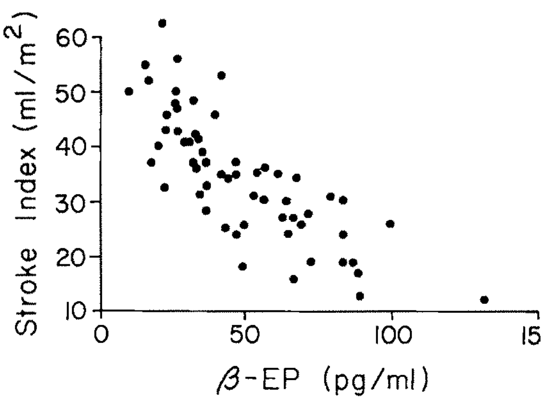

Figure 1. Scatter plot of stroke index (ml/m^2) versus immunoactive beta-endorphin (pg/ml) in preoperative cardiac surgical patients.

cutoffs as above) produced clear separations of associated hemodynamic measures (Table 3).

The strength of many of these relationships made it possible to derive formulas linking iBE and hemodynamic parameters. The relationships were first linearized by taking the natural logarithm of the dependent variable, iBE, and the results—along with 95% confidence limits—depicted in Figures 2A and 2B. Only the two most robust regression lines (i.e., for SI and PCW) are depicted, since variables less highly correlated with iBE (e.g., RAP) produced correspondingly greater scatter around regression lines.

Lastly, we examined whether correlations between iBE and hemodynamic indices were mainly due to contributions from the more decompensated patients, using SI = 40 ml/m^2 as the previously-derived cutoff value for "pump failure." As shown in Table 4, this proved to be the case: correlations between iBE and hemodynamics were uniformly more significant in patients with SI below 40 ml/m^2 than in those with SI above this value.

Discussion

Many investigators have studied the central effects of opiate systems in cardiovascular control (7,14–17), but the function of circulating opiopeptides is controversial. Certain clues point to an effect upon immunity (18), but such effects may not be relevant to the

Table 3. P-values (by ANOVA) for Segregation of Other Parameters When Patients Were Divided According to High Versus Low iBE or SI

	Sort on iBE	Sort on SI
iBE	(<0.001)	<0.001
SI	<0.001	(<0.001)
HR	<0.001	<0.001
MAP	0.501	0.611
Mean PA	<0.001	0.004
PCW	<0.001	<0.001
RAP	<0.001	<0.001
CO	<0.001	<0.001
CI	0.016	<0.001
SV	<0.001	<0.001
SVR	<0.001	0.002
PVR	0.001	0.005
BUN	0.242	0.676
CRE	0.560	0.983

ANOVAS were performed on untransformed data. Abbreviations as in Table 2A.

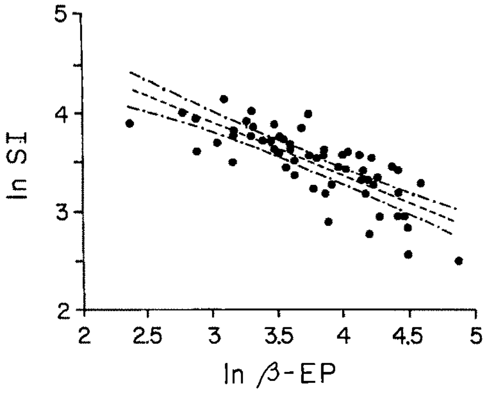

Figure 2A. Scatter plot of the natural logarithms of stroke index and immunoactive beta-endorphin in preoperative cardiac surgical patients. Ninety-five percent confidence limits for the regression line are drawn. The linear regression line formula is: ln SI = 5.7 − (0.60) (ln iBE).

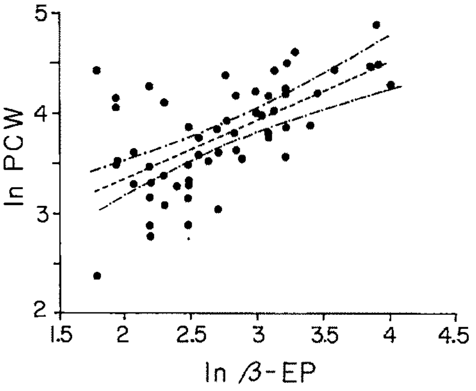

Figure 2B. Scatter plot of the natural logarithms of pulmonary capillary wedge pressure and immunoactive beta-endorphin in preoperative cardiac surgical patients. Ninety-five per cent confidence limits for the regression line are drawn. Linear regression line formula is: ln PCW = 1.7 + (0.79) (ln iBE).

patients we studied (in whom there were no clinical signs of infection). Several laboratories have recently described direct, peripheral effects of circulating opioids upon myocardial performance. Apparently conflicting effects may be observed depending upon the experimental model used: thus, in isolated myocytes, opioids enhance contractility (21,26), while in preparations in which cardiac innervation is preserved, their effects are chiefly to oppose catecholamine-induced contractility and chronotropy (19–20,22–25,27). This anti-catecholamine, modulatory effect is clearest when probed using the beta-adrenergic agonist isoproterenol (19,20,24), and is associated with a reduction in the normal calcium influx which ordinarily follows beta-agonist binding to myocardium (19,26). Conversely, peripherally administered opiate receptor antagonists such as naloxone or nalmephene acutely increase myocardial inotropy and chronotropy (22–24,27). The latter effects are particularly strong after acute bilateral carotid occlusion (24), or in chronic cardiac failure produced by tricuspid avulsion and progressive pulmonary artery constriction (27), both physiological states in which arterial pressure is especially dependent upon sympathetic outflow.

The above literature suggests that peripheral as well as central opioid pathways exert significant effects on the heart. The circuitry by which these effects occur, i.e., inhibition of underlying neurotransmission, mirrors that already recognized at many sites within the central nervous system, in which for example opioids inhibit substance *P* release (in dorsal horn of spinal cord), dopamine release (in hypothalamus or basal ganglia), or norepinephrine release (from locus coeruleus). Possible benefits of opiopeptide release upon the myocardium include reduction of vulnerability to ventricular fibrillation (28–30), and protection from other harmful effects of high circulating catecholamine levels (e.g., patchy necrosis) during circulatory compromise. Whether the increased blood levels of circulating iBE actually decrease inotropy or chronotropy enough to exert a protective effect upon myocardial oxygen consumption in these cardiac patients is speculative, although drugs which directly block beta-receptors or calcium channels are used clinically for just this purpose. Also, the in vivo biological specificity of cardiac opioid receptor-ligand interactions has not yet been determined.

The quantitative degree of our findings on the relationships between iBE and hemodynamic status was unexpected. Gann and colleagues (1) had earlier studied ACTH release in the cat during various

Table 4. Correlations Between iBE and Hemodynamics in Patients with SI Above or Below 40 ml/m^2

	Low SI (N = 44)		High SI (N = 21)		All patients (N = 65)	
	R	*P*	*R*	*P*	*R*	*P*
SI	−0.576	<0.001	−0.232	n.s.	−0.647	<0.001
HR	0.470	0.002	0.068	n.s.	0.578	<0.001
MAP	0.065	n.s.	0.251	n.s.	0.124	n.s.
Mean PA	0.310	0.048	0.441	n.s.	0.425	0.001
PCW	0.638	<0.001	0.531	0.023	0.702	<0.001
RAP	0.471	0.002	0.397	n.s.	0.535	<0.001
CO	−0.357	0.022	−0.222	n.s.	0.455	<0.001
CI	−0.187	n.s.	−0.050	n.s.	−0.316	0.015
SV	−0.591	<0.001	−0.355	n.s.	−0.643	<0.001
SVR	0.151	n.s.	0.317	n.s.	0.305	0.018
PVR	0.682	<0.001	0.495	n.s.	0.720	<0.001

Legend as for Table 2A.

semi-quantitative hemodynamic challenges, and our results are generally concordant. However, Gann and others have in various models found that acute arterial hypotension stimulates ACTH (1) and iBE (31,32) secretion, at variance with our insignificant correlations between iBE and MAP. We attribute this disparity to our having studied pre-intervention, presumably chronic levels of MAP rather than sudden decreases in MAP due to acute interventions, some of which, such as hemorrhage, lower CO and SI as well.

Recently, characterization of atrial natriuretic peptides (33,34) and development of radioimmunoassays for them have produced other quantitative results linking hemodynamic decompensation with increased secretion of a biologically active peptide (35–37). Secretion of these atrial peptides is regarded as a response to, rather than a cause of, cardiac dysfunction (33,34). Similarly, since experimental hemodynamic challenge is known to stimulate secretion of iBE (7,8,31), and administration of pharmacological quantities of exogenous beta-endorphin (25) is not recognized to produce cardiac dysfunction, we consider the elevations in iBE to be the result rather than the cause of decreases in SI. (In our patients, we found no evidence that decreased renal function, as reflected in CRE and BUN, led to artifactually elevated plasma iBE.) Much evidence indicates that atrial peptides are secreted as a compensatory reflex in response to fluid overload, and it is plausible that iBE secretion resulting from hemodynamic impairment is likewise a compensatory response. Nonetheless, the clinical significance of these iBE measurements, and their relation to assessments of longer-term functional status, remain unclear. Indeed, other peptides have recently been identified in nerves supplying the myocardium and coronary vasculature-substance P (38), vasoactive intestinal peptide (39), neurotensin (40), and neuropeptide Y (41)—and their clinical roles also await clarification. Our present results for iBE add to this growing literature on peptides in the periphery, and indicate that iBE secretion undergoes close, even quantitative regulation in the preoperative cardiac patient.

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ANESTH ANALG 83
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Caudal Anesthesia in Pediatric Surgery:

Success Rate and Adverse Effects in 750 Consecutive Patients

Bernard Dalens, MD and Abdou Hasnaoui, MD

DALENS B, HASNAOUI A. Caudal anesthesia in pediatric surgery: success rate and adverse effects in 750 consecutive patients. Anesth Analg 1989;68:83–9.

The success rate and occurrence of adverse effects are reported in a retrospective study of 750 caudal analgesias in children. In 94% of the patients, the blocks were performed under light general anesthesia. Standard IM or short-beveled needles were used in all. Four anesthetic solutions of lidocaine and/or bupivacaine with 1:200,000 epinephrine were injected in volumes ranging from 0.5 to 1.25 ml/kg. The overall success rate of caudal blocks was 96%, but several attempts were necessary in 25% of patients. Most failures occurred in children more than 7 years old. The use of short-beveled needles considerably decreased the number of traumatic punctures. The upper limit of analgesia varied widely and appropriate distribution of anesthesia was reliably obtained only after the injection of 0.75 to 1.0 ml/kg of local anesthetic solution. Conscious children tolerated surgery poorly (from a psychological point of view) although they were free of pain. Conversely, breathing difficulties occurred in 12% of lightly anesthetized patients. Hemodynamic disturbances were infrequent, as were adverse effects except for postoperative vomiting (17%). Motor block, present in 54% of patients, was poorly tolerated postoperatively by 10% of patients. Long-lasting postoperative pain relief was usually obtained. There were no major complications or neurological sequelae and good patient and parental acceptance of caudal anesthesia. Caudal anesthesia is a reliable and safe technique in young children.

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—caudal. ANESTHESIA, pediatric.

Caudal anesthesia has become increasingly widespread in pediatric surgery in recent years, especially for operations below the umbilicus. Since the first pediatric report in 1933 (1), several studies have described the indications for pediatric caudal block, the level of analgesia, recommended doses and pharmacokinetics of local anesthetics used in caudal anesthesia, and general or specific advantages and disadvantages of the technique (2–9). Only a few studies (9–12) have included large series of patients and their results are notably different, especially in regard to success rate and the frequency and severity of complications.

The purpose of this retrospective study was to evaluate the frequency of adverse effects and complications following 750 consecutive caudals blocks performed by two pediatric anesthesiologists using the same standard procedure. We report the correlation of these complications with the technique itself (type of needle used, site of injection), the selection and volume of local anesthetic, and the patient's age. The study data were obtained from the charts that were prospectively completed for each patient given a regional block in our unit using a procedure chart (completed by the anesthesiologist) and a recovery chart (completed by the nurse staff during the immediate postoperative period and by the surgeon at the postoperative visit 1 to 2 weeks later).

Materials and Methods

Between October 1982 and December 1987, 750 caudal blocks were performed in our pediatric unit in 416 boys and 252 girls. The children ranged in age from two days to 16 years. ASA physical status was 1 in 72%, 2 in 23% and 3 in 5% of patients. Surgical procedures included inguinal herniorraphies in 231 males and 178 females, 82 corrections of undescended testis, 77 hydrocelectomies, 47 circumcisions, 26 operations on the anus or rectum, and 77 miscellaneous procedures. In addition, 53 patients (7%) un-

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Address correspondence and reprint requests to Dr. Dalens, Pavillon Gosselin, Hôtel-Dieu B. P. 69, 63003 Clermont-Ferrand, France.

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derwent emergency operations of which 34 were for torsion of the testis. All blocks were performed after informed consent had been obtained from the parents and, as often as possible, from the children themselves.

Anesthetic Management

All procedures were carried out in operating rooms after insertion of an intravenous catheter and administration of atropine sulfate (0.02 mg/kg) and diazepam (0.05 to 0.1 mg/kg).

Most (704 or 94%) of the caudal blocks were performed under general anesthesia induced either by inhalation agents (halothane in 562, enflurane in 37 and isoflurane in 19 patients) or 4 mg/kg IV thiopental (when the children asked for intravenous anesthesia) (13,14). General anesthesia was discontinued after the caudal block in 19 patients and maintained in 685 with 0.25 to 0.5% halothane (or with equipotent concentrations of enflurane or isoflurane, when these halogenated agents were used for induction) in 65/35% N_2O/O_2. Patients breathed spontaneously without tracheal intubation as long as tidal volumes remained 0.9 ml/kg or above and end-tidal CO_2 43 mm Hg or below. Forty-six patients were not given general anesthesia.

The patients were placed in the lateral position with the operative side down. The caudal needle, initially inserted perpendicularly to the skin, was redirected and advanced rostrally for 2–3 mm after the sacrococcygeal membrane was penetrated with a characteristic "give." After absence of blood or cerebrospinal reflux was assured, a test dose (0.5 to 1 ml) was injected while the electrocardiographic tracings were scrutinized for at least 30 seconds. The injection was then completed within 60 to 90 seconds and the patient placed in the dorsal recumbent in the reverse Trendelenburg position.

Either a standard 21½ gauge 50 mm long IM needle (Becton-Dickinson®), or a 23 gauge 25 mm long short-beveled needle (designed according to our specifications by Eugédia®) (Figure 1) was used. In no instances were more than four attempts to enter the caudal epidural space made.

Four anesthetic solutions with 1:200,000 epinephrine were used: 0.5% lidocaine in 63 patients; 1.5% lidocaine in 35; 0.25% bupivacaine in 41; and a combination of 1% lidocaine and 0.5% bupivacaine in equal parts in 582 patients. The maximum doses were 2.5 mg/kg for bupivacaine and 10 mg/kg for lidocaine; the injected solutions ranged in volume from 0.5 to 1.25 ml/kg.

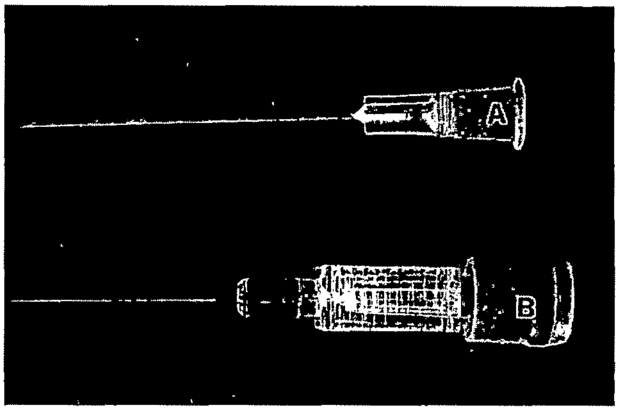

Figure 1. The two types of needles used in the study. A, standard 21½ gauge, 50 mm long, long bevel IM needle from Becton-Dickinson.® B, 23 gauge, 25 mm long, short bevel caudal needle designed according to our specifications by Eugédia.®

ECG tracings and respiratory rate were continuously monitored in all patients and blood pressure measured every three minutes by automated sphygmomanometer (Dinamap*). Tidal volume and end-tidal CO_2 were continuously monitored in patients given general anesthesia.

For each block procedure, the number of attempts, the technical difficulties and immediate adverse effects, if any, were recorded. Anesthetic latency, i.e., the time needed to achieve anesthesia at the site of incision, was evaluated by skin pinching every 5 minutes.

In patients given general anesthetics, the block was considered successful when the operation was performed without use of iv narcotics or sedatives or increases in the concentration of the inhalation agent administered. In patients not given general anesthetics, the success of the block procedure was evaluated on the basis of complaints of pain and restlessness.

Motor blockade was evaluated in the lower extremities either by asking patients to move their legs and/or by applying nociceptive stimuli aimed at eliciting withdrawal movements. Motor blockade was considered: 1) complete when the patient was unable to move any part of the lower extremity; 2) partial when there were withdrawal movements in the lower extremities but with weaker muscle strength than in the upper extremities; 3) absent in the presence of full strength movements of the lower extremities; and 4) asymetrical when both strength and range of lower extremity movements were different in the right and left legs.

The duration of the sensory block was measured as the time between injection and the first evidence of pain (complaints of pain; crying; grimacing; restlessness; or autonomic responses such as tachycardia, hypertension or sweating) occurring either spontaneously or with hourly assessments using skin pinching.

The children were not asked to void. The time at which the first postoperative micturition occurred was recorded and compared to the times of micturition following the peripheral blocks performed under the same conditions (including use of no narcotics) in our unit during the period from May 1985 to December 1987.

During the postoperative course, adverse effects, if any, were systematically recorded, as were complaints from patients, their parents and nurses. Patients were discharged from hospital after complete recovery of neurologic functions. At the time of postoperative visit, 8 to 17 days later, delayed adverse effects and neurological complications were carefully sought and, if present, recorded. In addition, parents were asked their overall impression about the anesthesia and whether they would or would not agree in the future that a caudal block be performed in one of their children.

Statistical Methods

Results, expressed as mean ± SD, were analyzed using nonparametric Mann-Whitney test. Qualitative variables were evaluated using chi-square test. Differences were considered statistically significant with $P < 0.05$.

Results

The caudal epidural space was entered on the first attempt in 530 patients (success rate: 70.6%) and after two to four attempts in 192 additional children (Table 1). The procedure was unsuccessful in 26 patients (failure rate: 3.5%) and this was significantly related to patient age: 19 of the 26 unsuccessful procedures occurred in 124 patients over 7 years of age, whereas only seven failures were encountered in the 626 patients less than 7 years old. In two additional cases (both in the IM needle group), the anesthetic solution was not injected due to repeated entry of the needle into blood vessels.

The most frequent cause of technical failure was subcutaneous insertion of the needle. This was not influenced by the type of needle used. On the other hand, entry of the needle into vessels occurred significantly more frequently with IM (10.6% of the times used) than with caudal needles (1.6% of the times used) (Table 1). In addition, one dural puncture and three inadvertent intravenous injections of the test dose (resulting in almost instantaneous cardiac dysrhythmia) occurred, all in the IM needle group (Table 1).

Table 1. Success rate and technical difficulties associated with caudal blocks

Events	IM needle (n = 386)	Caudal needle (n = 364)
Epidural entry		
On first attempt	269 (69.7%)	261 (71.7%)
After 2–4 attempts	100 (25.9%)	92 (25.3%)
Failure	17[a] (4.4%)	11 (3.0%)
Technical difficulties		
Subcutaneous insertion	72 (18.7%)	71 (19.5%)
Vascular penetration	41 (10.6%)	6 (1.6%)[b]
Intravenous injection of the test dose	3 (0.8%)	0 —
Dural puncture	1 (0.3%)	0 —
Overall difficulties	117 (30.3%)	77 (21.2%)[b]

[a] Includes 2 patients in whom the sacral hiatus was penetrated but who were not given local anesthetic due to repeated entry of the needle into blood vessels.

[b] Significant difference

The characteristics of the sensory block were significantly influenced by the local anesthetic (Table 2). The shortest latencies were produced by either 0.5% or 1.5% lidocaine and the longest by 0.25% bupivacaine, with intermediate latencies when a combination of 1% lidocaine and 0.5% bupivacaine was administered. The extent of the rostral spread of analgesia (Table 3) was positively correlated with the injected volume of local anesthetic. However, the final upper limit of sensory blockade varied widely from one patient to another with the same body weight-related volumes, especially in patients more than 7 years old. No mathematical formula was satisfactory for predicting the rostral limit of analgesia in individual cases.

The sensory block was symmetrically distributed on both sides of the body in 312 (43%) patients whereas the upper limit of analgesia was 1 to 2 dermatomes higher on the side on which the patient was lying during the block procedure in 354 (49%) cases. In 41 (6%) patients, the number of dermatomes blocked on each side differed by more than three and in 14 (2%) patients the sensory block was unilateral. A motor block developed in 389 (54%) of the 721 successful procedures. It was complete and bilateral in 107 (15%) patients, including 35 patients given 1.5% lidocaine (with 1:200,000 epinephrine), and lasted more than 3 hours in eight (1.1%). When incomplete, in 39% of patients, motor blockade lasted less than 3 hours in 34% and more than 5 hours in 2%

Table 2. Anesthetic latency

Anesthetic solution (n = 721)[a]	Latency			
	5 min	10 min	15 min	20 min
Lidocaine				
0.5% (n = 63)	39 (62%)[b]	24 (38%)[b]	—	—
1.5% (n = 35)	24 (69%)[b]	11 (31%)[b]	—	—
Bupivacaine				
0.25% (n = 41)	2 (5%)[c]	12 (29%)[c]	17 (41%)[c]	10 (24%)[c]
Lidocaine (1%) and Bupivacaine (0.5%) (n = 582)	213 (36%)	345 (59%)	29 (5)	—

[a]the 28 patients in whom the block was not completed and the one patient in whom a sensory block did not develop while the block procedure appeared successful, are not included in the evaluation.

[b]significant difference as compared to (1) patients given 0.25% bupivacaine only and (2) those given a combination of 1% lidocaine and 0.5% bupivacaine.

[c]significant difference as compared to patients given a combination of 1% lidocaine and 0.5% bupivacaine.

Table 3. Relation between the volume of the anesthetic solution and the spread of analgesia

	Volume of the Anesthetic Solution			
Spread of Analgesia	0.5 ml/kg (n = 50)	0.75 ml/kg (n = 50)	1 ml/kg (n = 626)	1.25 ml/kg (n = 26)
Appropriate (T11-T4)	62%[a]	82%	85%	67%[a]
Excessive (T4)	0%	0%	1%	29%[b]
Insufficient (T11)	32%[b]	16%[b]	8%[b]	0%[b]
Patchy block	4%	2%	4%	4%
Unilateral blockade	2%	0%	2%	0%
No anesthesia[c]	0%	0%	0.1%	0%
Mean height of block (± spinal segments)	T11 (1.5)	T10 (1.7)	T8 (1.6)	T5 (1.5)
Extreme upper limits	L3–T9	L1–T6	L1–T2	T8–T1

[a]significant difference as compared to patients given 0.75 or 1 ml/kg of local anesthetic

[b]significant difference as compared to the three other groups of patients.

[c]the block procedure appeared successful.

of cases. Lateralization of the motor block was observed in 32 (4.4%) patients.

Five patients were given another caudal anesthesia, with the same local anesthetic, 2 to 14 months after the first procedure. In these five cases, the upper limit of anesthesia was almost identical. Also, a caudal block was performed in four pairs of identical twins on the same day, and for the same operation. The same height of block was found in each pair of twins.

Of the 46 patients not given general anesthesia prior to the caudal block, 14 (30%) became restless and irritable 20 to 30 minutes after the start of the surgical procedures. Twelve of these patients were given general anesthetics to allow satisfactory conditions for completion of surgery. The 19 of the 704 anesthetized patients in whom anesthesia was discontinued during surgery did not require additional medication but six developed movements of the head and upper limbs at the end of the operation. Among the 685 patients lightly anesthetized during both the block procedure and the operation, 507 (74%) remained unresponsive throughout the operation, 119 (17%) showed increased respiratory rate and/or heart rate for less than 3 minutes, 46 (7%) moved in unanesthetized areas at the beginning of the operation, and 13 (2%) moved their lower limbs when the skin was incised. In all these patients, these responses lasted less than 4 minutes and no additional treatment was necessary.

Hypercapnia and a decrease in tidal volume below 0.9 ml/kg developed in 87 (12%) patients who were intubated (27 before the block procedure, 56 immediately before or very soon after the skin incision and the remaining four while the operation was in progress). Brief apnea developed in three: two had been given 1.25 ml/kg of local anesthetic and their upper limit of analgesia was above T3; the third was a premature baby. In all patients, heart rate and both systolic and diastolic blood pressures remained stable during surgery. The decrease in systolic pressure below levels measured prior to the block was less than 5% in 69.1% of patients; it ranged from 5% to 10% in 27.3%, and exceeded 10% in 3.6% of patients.

Table 4. Postoperative events (the numbers indicate the % of patients)

	Delay after injection				
Postoperative condition	1–2 h %	2–3 h %	3–4 h %	4–5 h %	5 h %
Behavior (n = 721)					
Quiet	77	80	85	90	97
Crying	16	15	12	10	3
Restless	7	5	3	—	—
Recovery of normal sensory functions					
0.5% lidocaine (n = 63)	17	67	16	—	—
1.5% lidocaine (n = 35)	6	40	45	9	—
0.25% bupivacaine (n = 41)	2	5	22	27	44
1% lidocaine + 0.5% bupivacaine (n = 582)	4	5	24	27	40
Adverse effects (n = 721)					
Vomiting	12	1	1.5	2	1
Pruritus	0.25	1	2.5	0.5	—
Fever (38.5°C)	—	—	—	1	1
Rashes	—	—	0.5	0.5	—
Shivering	0.5	—	—	—	—
Tingling	—	0.25	1.5	2.5	1.5

No vomiting or other adverse effects were observed during the operative period.

Postoperative Course

Most (703 or 97.5%) patients were discharged from the operating theater within 15 minutes after completion of surgery. Most (559 or 77.5%) children were quiet when returned to their bed and this increased to 97% by the fifth postoperative hour (Table 4). Some children (up to 16% at the second hour after surgery) were crying despite complete sensory blockade of the lower part of the body. About 7% of patients were anxious and restless (Table 4) when discharged from the operating room. Restlessness occurred later in 49 patients, especially in those with a motor block: only 9 (2.7%) of the 332 who had only a sensory block compared to 40 (10.3%) of the 389 who also had a motor block developed restlessness (significant difference).

The duration of the postoperative pain relief depended on the anesthetic solution (Table 4). The sensory block produced by 1.5% lidocaine lasted significantly longer than that produced by 0.5% lidocaine, and the block produced by 0.25% bupivacaine was longer in duration than that produced by 1.5% lidocaine. Duration of postoperative analgesia was similar when bupivacaine only and when the combination of bupivacaine with lidocaine was used.

Adverse effects, mainly nausea and vomiting (17% of patients), pruritus (5%), fever (2%), and cutaneous rashes (1%) were recorded in 179 (25%) patients. No respiratory or neurological disorders, no infection (either generalized or localized) and no fatalities occurred. Forty-two patients noted tingling in the legs during recovery from sensory block. The mean time to the first voiding was 5.85 ± 2.68 h, which was slightly but significantly longer than that after peripheral nerve blocks (4.93 h ± 1.83 h) (Table 5).

No sequelae were observed at the time of the postoperative visit and no adverse effects were spontaneously mentioned by parents. After questioning, tingling in lower limbs was mentioned in six cases the day after surgery. The overall evaluation of the procedure by the parents was favorable: no adverse opinion, 0%; "no opinion", 18%; "favorable", 66%; and enthusiastic, 16%. Each parent considered the technique acceptable in the event of a future operation.

Discussion

Caudal blocks are easy in children: the overall success rate was 96% in this study. However, difficulties were encountered in 25% of patients and in 4% the sacral hiatus could not be entered, more often in children older than 7 years (14.5% unsuccessful blocks in this group) than in younger patients. This may be related to developmental features. At birth, the sacrum is formed by five separate sacral vertebrae, mostly cartilaginous, and the sacral hiatus results from the incomplete fusion of the posterior arches of the fifth

Table 5. Delay between the caudal block and the first spontaneous voiding

Delay (hours)	Caudal Blocks		Upper Limb Blocks		Lower Limb Blocks	
	n	%	n	%	n	%
0 to 3	150	20.8	56	26.5*	37	21.4
3 to 6	275	38.2	98	46.5*	104	60.1*
6 to 9	225	31.2	55	26.1*	29	16.8*
9 to 12	71	9.8	2	0.9*	3	1.7*
Total	721	100.0	211	100.0	173	100.0

*Significant difference

and, frequently, the fourth sacral vertebrae. As the child grows, the posterior fusion becomes more complete, thus reducing the size of the sacral hiatus, while the sacral vertebrae fuse and ossify to form the adult sacrum (this is only achieved after 25 years). These anatomical changes, closely related to age, may account for the differences in the failure rate of caudal blocks reported in children, ranging from 2.8% (10) to 23.2% (1).

The use of short and short-beveled needles improved the success rate of caudal blocks by reducing inadvertent vascular penetrations: thus, danger of systemic toxicity is reduced by the use of such needles. In addition, these needles decrease the ease of penetration of cartilaginous structures of the sacrum, and, therefore, decrease the likelihood of complications such as bone marrow aspiration, intra-osseous injection or penetration into pelvic viscera. The use of needles longer than 25 mm is unnecessary and may lead to inadvertent penetration into the subarachnoid space (as occurred in one patient of our IM needle group), especially in neonates in whom the dural sac may project as low as the S3 vertebral body.

Several mathematical models aimed at predicting the upper limit of caudal analgesia have been reported (2,6,9,15). These models, however, are of little practical value in clinical practice since the height of the sensory block produced varies considerably from one patient to another. In our series, the administration of 1.25 ml/kg of local anesthetic, which has occasionally been recommended (16), led to excessive spread of analgesia in 30% of patients. Appropriate levels of analgesia were reliably produced in our patients only by the injection of 0.75 to 1 ml/kg of anesthetic solution (depending upon the site of surgery), as also reported by others (3,6,7,10). In addition, in almost 50% of our patients, the height of analgesia was 1–2 dermatomes higher on the side that was lowermost during the block procedure; this should be taken into account when determining the dose to be injected. Patchy anesthesia was unusual. Unilateral blockade developed in 2% of patients, probably due to the presence of a continuous median epidural band (17).

The spread of analgesia was more unpredictable in patients older than 7 years than it was in younger children. This might reflect a change in the consistency of epidural fat which becomes more densely packed by 7 years of age (3,18). The hypothesis that the fluidity of epidural fat might be the key factor in the spread of local anesthetic is supported by the fact that identical twins (i.e., presumably with the same consistency of epidural fat) given the same volume of anesthetic solution (on a weight-basis) had the same upper limit of sensory block. A change in consistency of the epidural content, due to inflammatory disorders has also been incriminated in the potential decrease in reliability of repeated caudal blocks. In this study, however, the spread of analgesia was the same in consecutive blocks, but the small number of patients does not permit us to conclude that the reliability of caudal blocks is not affected by previous caudal blocks.

The administration of general anesthetics to children undergoing a regional block is controversial, and it has been suggested that this is unnecessary in most patients (18). However, a number of our patients who accepted the caudal block as the sole anesthetic regimen were psychologically unable to tolerate the surgical procedure even though they usually tolerated without a major problem the block procedure itself (shorter in duration). On the other hand, light general anesthesia was associated with ventilatory problems in 12% of patients. Thus, either approach may have significant inconveniences.

In this series, 26% of patients had transitory physiological responses to skin incision. In all cases, they resolved spontaneously within 4 minutes. We ascribe these changes to a differential block resulting from the administration of diluted solutions of local anesthetics. Increasing the concentration of the local anesthetic would probably have blocked A alpha fibers more satisfactorily, thus reducing the occurrence of these responses, but this would also have increased the total dose administered and, thus, the potential for systemic toxicity (and the frequency of motor blocks).

Intraoperative hemodynamic status remained excellent in more than 95% of patients, in agreement with other reports in children (10,19). Adverse postoperative responses were infrequent, except for postoperative vomiting, which occurred 1 to 2 hours after the caudal block in 12% of patients. For reasons that remain unclear, the incidence of postoperative vomiting, as reported in the literature, varies widely, from 5% (10) to 37% (20). Delay in micturition following caudal blocks has been said to be more frequent than after penile blocks (20,21); this might be related to the site of injection since control of bladder function depends on sacral roots (S2 to S4). In the present study, while no patient required bladder catheterization, spontaneous voiding firts occurred slightly but (statistically) significantly longer after caudal blocks than after peripheral nerve blocks. The clinical significance of this difference is debatable since patients given peripheral blocks are usually older than those given caudal blocks.

The postoperative period was considered satisfactory by most parents, even when the children complained of residual motor block or nausea.

Caudal anesthesia is a reliable procedure in children younger than 7 years. The overall failure rate is slightly above 1% in these patients, compared to 14.5% in older children. The frequency of traumatic punctures is considerably reduced by using needles both short and short-beveled. Since the spread of local anesthetic solution and level of anesthesia vary widely from one patient to another, it is recommended that volumes of anesthetic solution exceeding 1 ml/kg not be administered. Motor blocks develop in some of children given caudal anesthesia, even when diluted solutions are injected, and it is poorly tolerated by about 10% of these patients. The block procedure and the operation are made easier when the patient is given light general anesthesia, but breathing difficulties may be encountered in up to 12% of cases. Postoperative adverse effects are infrequent, except for vomiting, and the first voiding usually occurs slightly later after caudal block than after peripheral block. The postoperative course following caudal anesthesia is smooth and most patients (75%) are quiet. No fatalities and no complications were observed. Parental and patient acceptance was good. Caudal anesthesia is a recommended technique in pediatric patients for operation below the level of the umbilicus and is well accepted by patients and their parents, most especially children younger than 7 years.

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Clinical Pharmacokinetics of Carbonated Local Anesthetics III: Interscalene Brachial Block Model

Radha Sukhani, MD and Alon P. Winnie, MD

SUKHANI R, WINNIE AP. Clinical pharmacokinetics of carbonated local anesthetics III: interscalene brachial block model. Anesth Analg 1989;68:90–3.

To compare serum levels of lidocaine resulting from 1.1% lidocaine carbonate and 1.0% lidocaine hydrochloride, the two salts were administered to ten healthy adult patients undergoing upper extremity surgery under interscalene brachial plexus block. Epinephrine (1:200,000) was added to both the solutions just prior to injection, and, following performance of the blocks, venous blood samples were drawn at 3, 5, 10, 15, 20, 30, 60 and 120 minutes. The concentration of lidocaine tended to rise more rapidly and to achieve higher levels in the first 10 minutes following injection of the carbonated lidocaine. However, no significant differences were found in the parameters of Cmax, Tmax or AUC for the two salts, and the serum levels in both groups at all times were well below the levels known to produce systemic toxicity. Therefore, while previous studies appear to indicate that the carbonate salt enhances diffusion, penetration, and uptake of neural tissues as compared with the hydrochloride salt, the present study indicates that vascular uptake is not similarly affected.

Key Words: ANESTHETICS, LOCAL: carbonated lidocaine. PHARMACOKINETICS, LOCAL ANESTHETICS: lidocaine.

Several clinical studies (1–3), including two recent studies by the present authors (4,5), have demonstrated that carbonated local anesthetics are associated with more rapid onset of action and greater extent of anesthesia than the equivalent hydrochloride salts when used for brachial plexus anesthesia. This has been attributed to more rapid diffusion and penetration resulting in greater neural uptake of carbonated local anesthetics (6–9). If so, then, at least theoretically, this increase in diffusion and penetration might also enhance vascular uptake and thus increase the possibility of systemic toxicity. Only three clinical studies (10–12) have addressed the possibility of enhanced vascular uptake by comparing blood levels of local anesthetics following injection of the carbonate and hydrochloride salts, and these studies yielded conflicting results. Furthermore, all three of these studies were carried out using the two local anesthetic salts for epidural anesthesia, a form of regional anesthesia in which many investigators have been unable to demonstrate any advantage derived from using the carbonate salt. Since all investigators (1–5) who have used lidocaine carbonate for brachial plexus anesthesia have clearly demonstrated that it produces a more rapid onset and greater extent of anesthesia than lidocaine hydrochloride, the present authors felt that a comparative study of blood levels following brachial plexus block with the two salts would provide more meaningful information if, indeed, vascular uptake does parallel neural uptake.

Methods and Materials

This study was carried out in ten healthy, consenting, ASA I and II patients scheduled to undergo upper extremity surgery under interscalene brachial plexus block. The ten patients were divided into two equal groups on the basis of which drug they were to be given: thus, Group I received 1% lidocaine hydrochloride, and Group II received 1.1% lidocaine carbonate. Equal volumes of 1% lidocaine hydrochloride and 1.1% lidocaine carbonate contain equivalent amounts of lidocaine base. Epinephrine was added to both local anesthetic solutions just prior to injection to a final concentration of 1:200,000.

Pre-anesthetic medication consisted of intramuscular or intravenous morphine in a dose that was

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Address correspondence and requests for reprints to Dr. Sukhani, Division of Pediatric Anesthesia, Cook County Hospital, 700 South Wood Street, Chicago, IL 60612.

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Table 1. Physical Characteristics of the Patients and Volume of Local Anesthetic Used

Lidocaine Preparation	Age (yrs) (Mean ± SD)	Height (in) (Mean ± SD)	Weight (kg) (Mean ± SD)	Volume (ml) (Mean ± SD)
Lidocaine-HCl	39.6 ± 20.4	69.8 ± 2.4	73.0 ± 8.5	38.6 ± 1.9
Lidocaine-CO$_2$	30.8 ± 5.8	69.6 ± 4.2	74.8 ± 9.3	37.4 ± 2.8

Table 2. Serum Concentrations (Venous Blood) of Lidocaine (µg/ml; mean ± SD)

Lidocaine	Time after Injection (in minutes)							
Preparation	3	5	10	15	20	30	60	120
Lidocaine-HCl n = 5	0.51 ± 0.21	0.65 ± 0.30	1.20 ± 0.48	1.63 ± 0.50	1.97 ± 0.71	2.15 ± 0.69	1.98 ± 0.48	1.53 ± 0.42
Lidocaine-CO$_2$ n = 5	0.82 ± 0.33	1.24 ± 0.56	1.54 ± 0.71	1.84 ± 0.66	1.82 ± 0.68	1.86 ± 0.46	1.74 ± 0.05	1.40 ± 1.14

individualized on the basis of weight and age. When each patient arrived in the operating room, an intravenous infusion was started in a saphenous vein, and a sphygmomanometer and ECG leads were applied. In addition, to allow periodic determination of venous lidocaine levels, an 18-gauge catheter was placed in the cephalic or basilic vein of the extremity contralateral to the one to be blocked. If local anesthetic was required for placement of the venous lines, 2-chloroprocaine was utilized. After venous blood had been drawn for the determination of "baseline lidocaine levels", an interscalene brachial plexus block (13) was carried out using a volume of local anesthetic in milliliters equal to half the patient's height in inches plus 2–4 milliliters. As soon as the injection was complete, a timer was started, and blood samples were drawn 3, 5, 10, 15, 20, 30, 60 and 120 minutes thereafter. The blood samples were immediately centrifuged and the serum refrigerated; later the serum was analyzed for lidocaine levels by the fluorescence polarization immunoassay technique (14,15). The intra- and interday coefficients of variation for the assay with replicate control samples was less than 5%, and the sensitivity of the assay was 0.05 µg/ml. The peak serum concentration (Cmax) and the time to peak serum concentration (Tmax) were determined by inspection of the data for each subject. The area under the serum-concentration time curve from time 0 to 120 minutes (AUC) was computed by trapezoidal rule. The data obtained in each group were compared using unpaired Student's *t*-test, and a *P* value of <0.05 was considered to be statistically significant. Verbal contact was maintained with the patients throughout the study to discern any symptoms that might be related to the systemic effects of the local anesthetic agent. Supplemental blocks of missed nerves, if necessary, were carried out 20 minutes following the initial block using a 1% solution of mepivacaine hydrochloride.

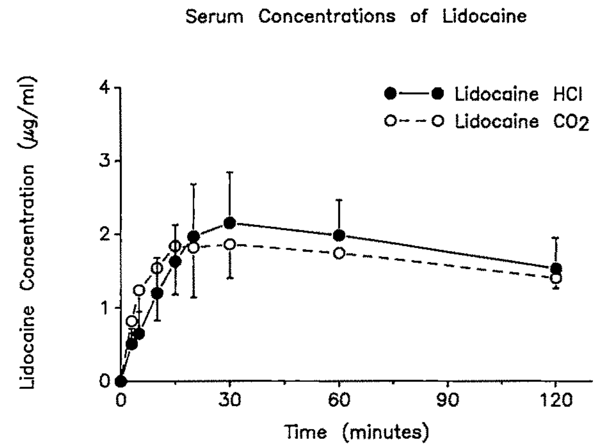

Figure 1. Time course of serum lidocaine levels (means ± SD of mean) following interscalene brachial block performed with lidocaine hydrochloride and lidocaine carbonate.

Results

The mean age, height, and weight of the patients in the two groups and the mean volume of local anesthetic used did not differ significantly (Table 1). Table 2 compares the serum lidocaine levels in the two groups at various time intervals following the block, and Figure 1 represents these data graphically. Although the mean serum lidocaine levels were higher in the carbonate group during the first 15 minutes and higher in the hydrochloride group thereafter, these differences were never statistically significant. Table 3 compares the pharmacokinetic parameters of the two lidocaine preparations. No significant differences were found for Cmax, Tmax and AUC. Further-

Table 3. Pharmacokinetic Parameters of the Two Lidocaine Salts (mean ± SD)

Parameter	Lidocaine HCl n = 5	Lidocaine CO_2 n = 5
Cmax (μg/ml)	2.21 ± 0.61	2.16 ± 0.38
Tmax (minutes)	31 ± 17	29 ± 18
AUC_0^{120} (μg-hr/ml)	211.0 ± 53.9	191.7 ± 21.8

Cmax = peak serum concentration.
Tmax = time of peak serum concentration.
AUC_0^{120} = area under the serum concentration-time curve from time 0 to 120 minutes.

more, while lidocaine was detectable throughout the entire 2-hour period in both groups, the levels were well below the toxic range; and none of the patients in either group reported any symptoms suggestive of clinical toxicity.

The supplemental blocks which were administered are tabulated in Table 4. In the carbonate group 3 out of the 5 patients required supplemental blocks, while all of the patients in the hydrochloride group required them.

Discussion

Systemic toxic reactions resulting from high blood levels of local anesthetics are a major concern in regional anesthesia. Such levels can result either from inadvertent intravascular injection or from the absorption of excessive amounts of local anesthetics injected appropriately. The factors known to influence the rate of absorption of local anesthetics from the site of injection include the rate of injection, the total dose of the drug, the anatomical site at which the injection is made, the vascularity of that site, and the rate of release of the local anesthetic base (16). In the case of a carbonate salt of a local anesthetic, the last two factors may be of greater importance because the carbon dioxide released following injection may produce local vasodilatation; this should increase the rate of absorption. In addition, as the carbon dioxide released from the injectate diffuses away from the site of injection, there is a resultant increase in pH, which should increase formation of free base, the form of the local anesthetic which readily diffuses across biological membranes and facilitates neural and vascular uptake.

As mentioned earlier, two of the three epidural studies comparing blood levels following the injection of the carbonate and hydrochloride salts of local anesthetics, Martin et al. (10) using lidocaine and Appleyard et al. (12) using bupivacaine, found the blood levels of local anesthetic to be significantly higher following the administration of carbonated salts. However, in the study by Appleyard et al. epinephrine was added only to the hydrochloride salt and was omitted from the carbonate preparation. Thus, in their study the higher blood level of lidocaine seen when the carbonate form was used is simply because of the addition of epinephrine to the hydrochloride, which decreased vascular uptake in that group. The absolute blood levels of lidocaine were higher in the study by Martin et al. (10) than in the study by Nickel and Bromage (11), although the former authors employed lower doses of lidocaine, compared to the latter. This also could be due to the fact that Martin et al. determined arterial lidocaine levels, while Appleyard et al. determined venous levels, and arterial levels are known to be almost 25% higher than venous levels (17). The epidural study by Nickel and Bromage, also compared the carbonated preparation with the hydrochloride preparation (both with epinephrine 1:200,000) and indicated that the carbonate salt resulted in higher blood levels of lidocaine in the first 20 minutes following the injection, the difference between the two was not statistically significant.

In our study comparing the blood levels when the two salts of lidocaine were utilized for brachial plexus block, we used doses of lidocaine almost identical to those used by Nickel and Bromage in the epidural study; and the pattern of blood levels produced by each agent were quite similar in both studies. The similarity of the blood level patterns in the two studies would seem to indicate that the absorption characteristics of local anesthetics from the interscalene space may be similar to that of the epidural space.

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Capnography Is Not as Sensitive as Pulmonary Artery Pressure Monitoring in Detecting Marrow Microembolism

Studies in a Canine Model

Robert J. Byrick, MD, FRCPC, J. Colin Kay, AIMLT, and J. Brendan Mullen, MD, FRCPC

BYRICK RJ, KAY JC, MULLEN JB. Capnography is not as sensitive as pulmonary artery pressure monitoring in detecting marrow microembolism: studies in a canine model. Anesth Analg 1989;68;94–100.

We studied several methods for detecting pulmonary embolic events in a model of fat and marrow microembolism during canine cemented arthroplasty procedures. The cardiopulmonary effects of bilateral cemented arthroplasty in this model include increased pulmonary artery pressure and pulmonary vascular resistance accompanying a decrease in arterial oxygen tension. We documented significant fat and marrow microembolism by postmortem quantitative morphometry of lung sections. Vessels occluded ranged in diameter from 0.5 to 190 microns.

The acute increases in pulmonary artery pressure (PAP) (to 26.8 ± 4.4 mm Hg from 15.3 ± 3.3 mm Hg) after cemented arthroplasty were not detected by changes in continuously monitored end-tidal CO_2 or in right atrial or arterial blood pressures. Although capnography is a useful intra-operative monitor, in this model it is less sensitive than PAP monitoring in detection of fat and marrow microemboli.

Key Words: EMBOLISM—fat, marrow. MEASUREMENT TECHNIQUES—capnography. MONITORING—capnography.

Marrow and fat microembolism is an infrequent but potentially fatal complication of cemented arthroplasty procedures (1–3). We have simulated a cemented arthroplasty procedure in anesthetized mongrel dogs (4) and documented the cardiopulmonary changes which are produced. Pulmonary dysfunction in this model is characterized by increased pulmonary artery pressure (PAP), and pulmonary vascular resistance (PVR), together with decreased arterial oxygen tension (PaO_2) and pathological evidence of pulmonary fat and marrow microembolism (4).

The purpose of this study was to evaluate the usefulness of monitoring end-tidal CO_2, which sensitively detects venous air embolism (VAE) (5,6), as compared with immediate changes in hemodynamic function in the detection of fat and marrow microembolism during cemented arthroplasty.

Methods

Twelve large mongrel dogs weighing 25 to 35 kg were anesthetized with pentobarbital 30 mg/kg intravenously followed by a continuous infusion of pentobarbital 5 $mg \cdot kg^{-1} \cdot hr^{-1}$. The tracheas were intubated and the lungs mechanically ventilated with a nonrebreathing circuit using room air. Ventilation was adjusted prior to any surgical procedure resulting in a tidal volume of 15–20 ml/kg at a rate of 8–10 breaths per minute to keep arterial PCO_2 ($PaCO_2$) at 35–40 mm Hg. Lactated Ringer's solution, approximately 10 $ml \cdot kg^{-1} \cdot hr^{1}$ was administered intravenously.

A 7 French triple-lumen balloon tipped pulmonary artery (PA) catheter was inserted into the left femoral vein and positioned in the pulmonary artery to continuously measure both the PAP and right atrial pressure (RAP). Thermodilution cardiac output ($\dot{Q}$) was measured in triplicate using the Edwards Laboratory Model 9510 cardiac output computer. The mean value of Q was calculated for each measurement period. The left femoral artery was cannulated to measure systemic arterial blood pressure (BP). A Cordis 7F pigtail catheter was inserted into the left carotid artery and advanced retrogradely through the

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Address correspondence and reprint requests to Dr. Byrick: Dept. of Anaesthesia, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1W8.

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left ventricle to the left atrium to monitor pressure (LAP) continuously.

A sampling catheter was placed in the lumen of the endotracheal tube to sample expired gas from the distal end of the endotracheal tube. The sampling catheter was connected to a calibrated Beckman LB-11 infrared carbon dioxide analyzer for determination of the percentage of carbon dioxide at end expiration ($P_{ET}CO_2$).

Samples of arterial and mixed venous blood (from the pulmonary artery catheter) were obtained for measurement of blood gas tensions (PCO_2, PO_2, pH). All values were corrected for body temperature. Mixed expired gases were collected using a one-way valve attached to the endotracheal tube and analyzed for oxygen and carbon dioxide concentration. Intrapulmonary shunt fraction (Qs/Qt) and the ratio of physiological deadspace to tidal volume (V_D/V_T) were calculated using standard equations (7,8). Oxygen consumption and CO_2 production were also calculated.

The operative procedure utilized a lateral parapatellar exposure of both distal femurs with dislocation of each patella medially. Both femoral canals were drilled and reamed retrogradely to a depth of 10 cm. using successively larger reamers (Pohl-Howmedica) until a size 9 reamer was readily inserted. Low viscosity bone cement was then injected into both femoral intramedullary canals under manual pressure and solid, contoured metal prostheses were immediately hammered into place.

Baseline measurements of $\dot{Q}$, Qs/Qt and V_D/V_T were made after exposure and reaming of both femora. As well, representative values of arterial BP, PAP, RAP, LAP and $P_{ET}CO_2$ were sampled and recorded continuously at the time $\dot{Q}$ was measured.

During and for two minutes after cement and prosthesis insertion (Figure 1), the arterial BP, PAP, LAP, RAP and $P_{ET}CO_2$ were continuously recorded. The measured value of each of these variables at specific time intervals (30, 60 and 120 seconds) after cement insertion (Figure 1) were recorded. An arterial blood sample was obtained from the femoral arterial cannula one minute after cement insertion (Fig. 1) and analyzed for PO_2, PCO_2 and pH. All hemodynamic measurements (continuously monitored pressures as well as intermittent values of Q, Qs/Qt and V_D/V_T) were repeated 5, 15, 30 and 60 minutes after cement insertion.

While still anesthetized, the dogs were killed after the 60-minute measurements were made by injecting potassium chloride through the left atrial line. The chest was opened immediately and the pulmonary vessels ligated. The heart and lungs were removed en bloc. The lungs were fixed in inflation with 10% buffered formalin at a pressure of 25 cm H_2O. After fixation for 72 hours the lungs were sectioned sagittally and three stratified random blocks of known size were taken from the midsagittal slice of each lung. Samples were post-fixed in Flemmings solution for 72 hours followed by washing in running water for 24 hours. Samples were processed for histological examination in the usual manner, then cut at 5-micron thicknesses. Morphometric measurements were performed on the six lung specimens from each dog using a camera lucida and an IBM-PC computer assisted digitizing board. The number of fat emboli and area of lung occluded from twelve random fields (each 1 mm^2) were determined for a total lung area of 72 mm^2 per animal. The mean diameter of the vessels occluded was also measured.

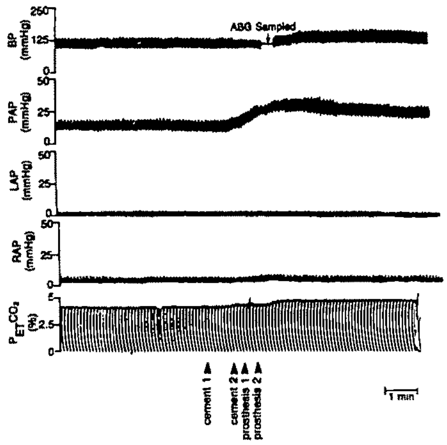

Figure 1. Sample trace from one dog studied showing changes in continuously monitored variables: arterial blood pressure (BP), pulmonary artery pressure (PAP), left atrial pressure (LAP), right atrial pressure (RAP), and end-tidal CO_2 ($P_{ET}CO_2$) during cement and prosthesis insertion.

In two additional animals, we collected the particulate marrow debris resulting from manual lavage of both intramedullary cavities after reaming. We then infused this marrow material in 50 ml of normal saline into a large-bore left femoral vein cannula (14 gauge) while monitoring arterial BP, RAP, PAP, LAP and $P_{ET}CO_2$. The purpose of performing these experiments was to determine the ability of the monitors to detect a known marrow embolic event.

In three additional dogs, approximately 10 grams of 60–110 micron glass beads were infused to produce a pulmonary vascular lesion (elevated PAP and PVR). With stable PAP and Q, the femurs were then drilled and reamed, and bilateral cemented arthroplasties were performed while monitoring arterial BP, PAP and $P_{ET}CO_2$. The purpose of this study was to demonstrate the hemodynamic consequences of cemented arthroplasty in dogs with compromized car-

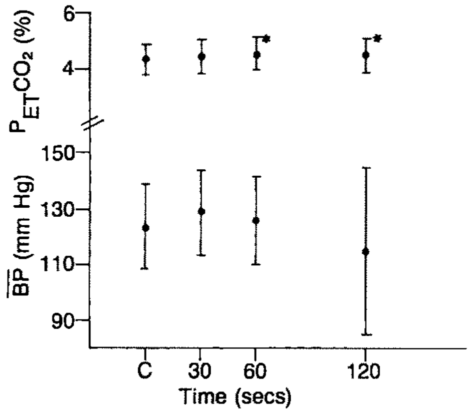

Figure 2. Mean values (±SD) of arterial blood pressure (BP), and end-tidal CO_2 ($P_{ET}CO_2$), at 30, 60 and 120 seconds after cement and prosthesis insertion.

diopulmonary reserve and to assess the usefulness of monitoring end-tidal CO_2 in this situation.

All femora used in the study were removed and radiographically examined to verify prosthesis location, and absence of fracture.

Mean values are reported plus or minus one standard deviation (SD). Differences between baseline values and those following implantation of cement were analyzed using a two-way analysis of variance without replication (9) and Dunnett's multiple range test with a significance level of 0.05.

Using the standard error of our change in $P_{ET}CO_2$ and a minimal expected change in $P_{ET}CO_2$ of 0.5%, based on English's data, (5), we determined the probability of missing a 0.5% decrease in end-tidal CO_2, that is the chance of making a Type II error.

Results

Figure 1 shows the immediate hemodynamic and end-tidal CO_2 responses to the bilateral cemented arthroplasty procedure in one animal. Mean values (±1 SD) of BP, PAP, RAP as well as $P_{ET}CO_2$ in 12 dogs 30, 60 and 120 sec after cement and prosthesis insertion are shown in Figures 2 and 3. No differences from baseline values in BP, RAP, or LAP were found; however, significant increases in PAP from initial values of 15.3 ± 3.3 mm Hg to 23.1 ± 5.7 and 26.8 ± 4.4 mm Hg occurred 60 and 120 seconds after cement insertion (C in Fig. 1). A PAP increase of at least 6 mm Hg occurred in every animal (range 6–19 mm Hg). No significant change in $P_{ET}CO_2$ was detected at the 30 second interval (Figure 2) and in only 1 of 12 dogs did $P_{ET}CO_2$ decrease (5.0 to 4.75%) after cement and prosthesis insertion. At the 60- and 120-second measurement (Figure 2) $P_{ET}CO_2$ increased to 4.5% from 4.4% ($p < 0.05$).

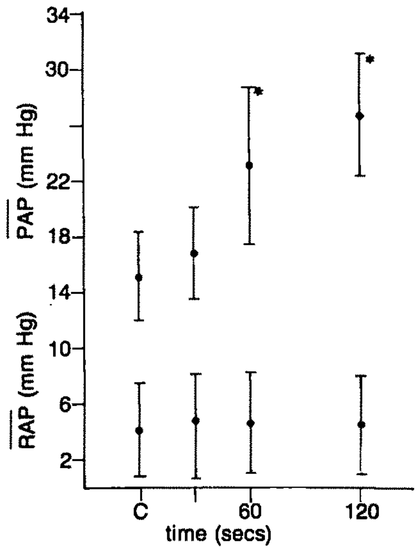

Figure 3. Mean values (±SD) of pulmonary artery pressure (PAP) and right atrial pressure (RAP) in 12 dogs measured 30, 60 and 120 seconds after cement and prosthesis insertion.

Measurements made at 5-, 15-, 30- and 60-minute intervals (Table 1) demonstrated no significant differences from baseline mean values in $\overline{BP}$, $\overline{RAP}$ or $\overline{LAP}$ and a slight decrease in $\dot{Q}$ at the 60-minute measurement.

Calculated values of systemic (SVR) and pulmonary vascular resistance (PVR) (Table 1) showed a significant increase in PVR from 200 ± 104 dyne·sec·cm^{-5} to 496 ± 164 dyne·sec·cm^{-5} five minutes after cement and prosthesis insertion. This elevated PVR occurred without any significant change in $\dot{Q}$ over the first 30 minutes and persisted throughout the study (Table 1). A small increase ($p < 0.05$) in SVR was present 15, 30 and 60 minutes after the arthroplasty was performed (Table 1).

No differences from baseline measurements were found in V_D/V_T at 5, 15, 30 or 60 minutes after cemented arthroplasty (Table 2); however Qs/Qt (Table 2) increased significantly above baseline values at all measurement times after insertion of cement. Significant oxygen desaturation of hemoglobin was also detected at all measurement intervals as well as decreases in PaO_2 and $P\bar{v}O_2$ (Table 2). No changes from baseline measurements in mixed venous PCO_2 ($P\bar{v}CO_2$), CO_2 production or O_2 consumption were detected (Table 2) at any of these measurement periods. Arterial PCO_2 ($PaCO_2$) increased significantly above baseline (to 38.6 ± 3.9 from 36.8 ± 3.9) at the 5 minute period as well as one minute after cement insertion (38.2 ± 2.8 mm Hg).

The size distribution of lung vessels occluded by fat microemboli is represented as a histogram (Fig. 4).

Table 1. Intermittent Measurements of Cardiovascular Variables After Cement and Prosthesis Insertion in Twelve Animals

	Baseline	5 min.	15 min.	30 min.	60 min.
$\overline{BP}$ (mm Hg)	123.9 ± 15.5	126.2 ± 26.2	130.3 ± 17.3	135.4 ± 16.3	135.7 ± 16.7
$\overline{RAP}$ (mm Hg)	4.3 ± 3.4	4.3 ± 3.4	4.9 ± 3.9	3.9 ± 3.7	4.2 ± 3.9
$\overline{PAP}$ (mm Hg)	15.3 ± 3.3	26.4 ± 4.6*	22.6 ± 2.9*	22.8 ± 3.1*	21.9 ± 3.5*
$\overline{LAP}$ (mm Hg)	7.3 ± 3.1	8.1 ± 4.2	7.8 ± 3.7	8.1 ± 4.2	7.8 ± 3.6
$\dot{Q}$ (L/min^{-1})	3.4 ± 1.1	3.2 ± 1.1	3.2 ± 1.3	3.2 ± 0.9	3.0 ± 1.1*
SVR (dynes/sec/cm^{-5})	3072 ± 998	3336 ± 1092	3512 ± 1299*	3496 ± 866*	3904 ± 1064*
PVR (dynes/sec/cm^{-5})	200 ± 103	496 ± 164*	408 ± 186*	392 ± 126*	416 ± 149*

Values are reported as mean ± one SD
*indicates significant difference from baseline

Table 2. Intermittent Measurements of Gas Exchange Variables After Cement and Prosthesis Insertion in Twelve Animals

	Baseline	5 min.	15 min.	30 min.	60 min.
PaO_2 (mm Hg)	95.0 ± 11.7	84.6 ± 10.9*	81.2 ± 12.6*	81.6 ± 12.5*	82.2 ± 12.8*
SaO_2 (%)	91.9 ± 1.6	90.2 ± 2.3*	89.7 ± 3.0*	89.8 ± 2.8*	90.1 ± 2.7*
Qs/Qt (%)	23.4 ± 6.4	28.7 ± 7.0*	29.0 ± 8.3*	28.4 ± 8.0*	28.3 ± 8.7*
V_D/V_T (%)	54.3 ± 5.2	54.5 ± 5.1	52.3 ± 6.6	51.4 ± 6.1	52.2 ± 7.6
$P'vO_2$ (mm Hg)	49.9 ± 6.3	47.7 ± 7.2	44.3 ± 6.5*	43.7 ± 5.9*	42.8 ± 5.3*
$S'vO_2$ (%)	73.3 ± 3.8	72.1 ± 5.7	70.1 ± 5.6*	69.6 ± 5.9*	69.7 ± 5.2*
O_2 Consumption (ml/min)	146.8 ± 36.7	160.0 ± 50.8	159.3 ± 47.1	159.6 ± 41.4	148.1 ± 42.0
$PaCO_2$ (mm Hg)	36.8 ± 3.9	38.6 ± 3.9*	36.1 ± 3.6	36.3 ± 3.4	36.0 ± 3.5
CO_2 Production (ml/min)	128.0 ± 27.8	134.9 ± 36.1	132.1 ± 36.5	135.2 ± 32.5	131.2 ± 34.8
$P'vCO_2$ (mm Hg)	42.6 ± 3.7	44.8 ± 4.5	43.2 ± 4.4	43.5 ± 4.9	43.5 ± 3.7

Results are reported as mean ± one SD
*indicates significant difference from baseline

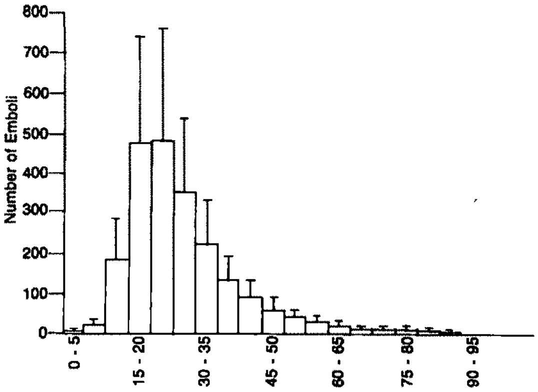

Figure 4. Six random midsagittal lung slices were processed for histological examination. Morphometric measurements were made on twelve random fields (1 mm^2) per slice for a total lung area of 72 mm^2 per animal. The total number of emboli counted in vessels of various diameters are shown.

Vessels occluded ranged in diameter from 0.5–190 microns. The mean percentage of lung volume occupied by fat microemboli ranged from 0.3 to 3.4% (mean 1.5 ± 0.9%).

When particulate marrow debris was collected from the reamed medullary cavities and infused into two animals PAP increased from 24 to 26 mm Hg and from 22 to 30 mm Hg with simultaneous transient decreases in $P_{ET}CO_2$ from 4.1 to 3.8 and 4.75 to 4.2%. Quantitative morphometry of the lungs of these two animals showed a similar distribution of fat emboli in the lungs with the exception that larger vessels (>190μ diameter) were occluded. These vessels accounted for less than 1% of the total number of emboli, but were not observed in the cemented arthroplasty group (Figure 4).

In three animals who had bilateral cemented arthroplasties after the infusion of 60-110μ glass beads, a profound hypotension (Table 3) developed along with elevated PAP, reduced $\dot{Q}$ and a subsequent decrease in $P_{ET}CO_2$ (Table 3).

Radiographic examination of all femora revealed no fractures during implant insertion.

Discussion

In this study pulmonary arterial pressure monitoring detected a sudden increase in PAP (Figs. 1, 3) immediately after cement and prosthesis insertion in

Table 3. Measured Values of Arterial Blood Pressure (BP), Pulmonary Artery Pressure (PAP), and End-Tidal CO_2 ($P_{ET}CO_2$) in Three Dogs Having Cemented Arthroplasty After Glass Beads (60–110 microns) Had Been Injected. Measurements Reported Before (Baseline) and 30, 60, and 120 Seconds After Cement Insertion.

	Dog No.	Baseline	30 sec	60 sec	120 sec
$\overline{BP}$ (mm Hg)	1	130	38	35	25
	2	110	58	62	58
	3	122	63	75	128
$\overline{PAP}$ (mm Hg)	1	23	44	44	30
	2	34	53	54	51
	3	28	55	57	51
$P_{ET}CO_2$ (%)	1	4.05	1.80	0.75	0.25
	2	3.90	3.45	3.20	3.05
	3	3.45	3.25	3.30	3.50

twelve dogs that was not reflected in a simultaneous decrease in end-tidal CO_2 (Fig. 2). These data contrast with both clinical (10) and experimental (5,6,11) studies using VAE models. The absence of changes in LAP indicate that these increases in PAP did not result from left ventricular dysfunction and reflected instead increased PVR (Table 1). The hemodynamic measurements during the next 60 minutes show that these changes in PAP and PVR were sustained for at least one hour after cement and prosthesis insertion, similar to our clinical experience (1).

Unlike VAE experiments, the quantity of marrow microemboli in this model is uncontrolled. Pathologic examination of the lungs using morphometric measurements estimated that the total area of lung tissue occupied by fat was approximately 1.5% of total lung volume. The total capillary volume accounts for approximately 8% of total lung volume (12). Therefore, we estimate that approximately 20% (1.5/8) of lung capillaries were occluded by fat microemboli in our dogs. Since 92% of vessels occluded were less than 50μ in diameter (Figure 4) and 99% of vessels occluded were less than 75μ, few precapillary arterioles were blocked. This distribution (Fig. 4) duplicates that of vessels occluded in one patient who died of massive fat and marrow microembolism whose lungs at post-mortem were examined using the same morphometric technique (2). Since approximately 50% of the lung's total vasculature should be occluded to increase PAP (13), active pulmonary vasoconstriction must augment the physical obstruction from microemboli. Pulmonary arterial hypertension has been described in other models with less than 50% obstruction of the vascular bed when emboli are less than 170μ in diameter (13). We have previously reported that drilling and reaming of both femora alone resulted in only 0.07 volume % of lung tissue occluded (4). This represents only 3% of the emboli found in this study which suggests that pressurization of the intramedullary canal by cement and prosthesis insertion, not the reaming process, is responsible for pulmonary fat embolism.

The fundamental discrepancy in $P_{ET}CO_2$ response between our data and those using VAE (5,6) could result from a difference in the site and size of vessels occluded. Young et al (14) used spherical polystyrene beads of specific diameter (range $50–500\mu$) to determine the size of the canine functional gas exchange unit. Their multiple inert gas elimination data (14) demonstrated that beads of $50–100\mu$ diameter never produced high V_A/Q regions; whereas 150, 200 and 500μ beads consistently induced increased deadspace. They concluded that the functional gas exchange unit in the dog lung is that volume perfused by 150μ diameter vessels which are associated with respiratory bronchioles. Thus, shifts of perfusion caused by fat and marrow microemboli smaller than 150μ (as in our model) could result in re-distribution of perfusion within a functional gas exchange unit of the lung, preserving CO_2 excretion within the unit (hence $P_{ET}CO_2$ levels), albeit at higher PAP.

When the reamed contents of the intramedullary cavity were collected and infused intravenously in two animals both PAP monitoring and capnography detected the embolic event. Quantitative morphometry showed a small number (0.5% of total) of emboli larger than 150μ diameter. This suggests that the particulate contents of the reamed cavity may be filtered prior to reaching the systemic venous circulation during cemented arthroplasty preventing large particulate embolization. The size of the medullary vessels opened during the reaming process may be the limiting factor determining the diameter of marrow particle capable of being forced into the venous circulation during the pressurization process. The sensitivity of capnography and PAP monitoring appear to be similar for larger particulate marrow infused intravenously after lavage of the reamed canal since small increases in PAP (2 and 8 mm Hg) corresponded to decreases in $P_{ET}CO_2$ of 0.3 and 0.55%.

Microemboli with a specific gravity similar to that of the formed elements in blood, such as fat microemboli, are distributed relative to regional blood flow (13). Air emboli, however, have been shown to preferentially embolize the nondependent lung zones (15). This distribution of air emboli, by increasing deadspace in the non-dependent lung regions, might also explain the sensitivity of $P_{ET}CO_2$ in VAE, as compared to fat microembolism, when Q is maintained at baseline levels (Table 1) in both instances.

English et al. (5) found that 0.5 ml/kg of air injected intravenously produced a decrease in $P_{ET}CO_2$ of at least 0.5% and an increase in PAP of 3 mm Hg in 100% of anesthetized dogs. They (5) did not demonstrate a significant change in Q with this volume of air. In our dogs, Q had not changed significantly 3–5 minutes after prosthesis insertion and PAP increased immediately (Fig. 3). Unlike VAE the embolic event was not detected by $P_{ET}CO_2$ monitoring (Figure 2). If we assume that a change of 0.5% $P_{ET}CO_2$ should have been detected based on English's data (5) the probability of having committed a type II error is less than one percent. Therefore it is highly unlikely that a true decrease in $P_{ET}CO_2$ was missed in our experiments.

In another VAE study (6), one ml/kg of air administered intravenously to mongrel dogs produced an increase in mean PAP to 21.0 from 13.7 mm Hg and a decrease of $P_{ET}CO_2$ in every animal (from a mean of 4.13 ± 0.7 to 3.37 ± 0.5%). These PAP changes are similar to those found in our study (Fig. 3); however we detected no decrease in end-tidal CO_2 level. Therefore, VAE is unlikely to be the cause of cardiopulmonary dysfunction in this model.

It is clear that the maintenance of $P_{ET}CO_2$ was not secondary to a prolonged increase in CO_2 production or $P\bar{v}CO_2$ level (Table 2), as these values were unchanged at the five minute measurement. The transient increase in $PaCO_2$ (Table 2) and $P_{ET}CO_2$ (Figures 1 and 2) after the cemented arthroplasty procedure, without any change in ventilation, could potentially result from a transient increase in venous PCO_2, perhaps emanating from heated bone.

The measurement of V_D/V_T is not a reliable index of the degree of vascular obstruction in microembolism as ventilation also is re-distributed to maintain matching of ventilation and perfusion (16). We expected that an immediate, transient change in $P_{ET}CO_2$ simultaneous with elevated PAP might occur after a sublethal embolic insult, and this transient effect might be missed by measuring V_D/V_T at 5 minutes after prosthesis insertion as in previous studies (4,17).

One clinical study has detected sublethal marrow embolism (18) during cemented arthroplasty with similar increases of PAP (to 25 ± 3 from 17.1 mm Hg) and end-tidal CO_2 decreased (to 29 ± 3 from 35 ± 4). Our data suggest that PAP increases may detect microembolism before end-tidal CO_2 changes. Patients with limited cardiopulmonary reserve (1), as in the animals studied after glass beads had been infused (Table 3), can have catastropic cardiovascular collapse. The reduced $P_{ET}CO_2$ reported by Roewer et al (18) in response to cemented arthroplasty may well reflect a decrease in cardiac output. The unknown incidence of the syndrome clinically precludes routine PAP monitoring, thus the clinician must be aware of the potential problems and have a high index of suspicion in high-risk patients (1,4). Such monitoring techniques as pulse oximetry (1) and transcutaneous oxygen analysis (19) would detect hypoxemia (Table 2). Doppler ultrasound (3) or transoesophageal echocardiography (18) detect "chirps" or "flakes" reflecting marrow microemboli.

In a recent clinical study (20), Doppler ultrasound detected emboli in 22 of 36 patients having cemented hip arthroplasty. Arterial PO_2 decreased and $PaCO_2$ increased by the 5-minute measurement time, as in our animals. The $P_{ET}CO_2$ decreased by only 0.1% from 4.8 ± 0.1 to 4.7 ± 0.1 percent in these patients having cement inserted by syringe. Neither PAP nor $\dot{Q}$ were monitored in that study (20).

Although capnography should be used in monitoring during cemented arthroplasty procedures, the clinician cannot assume that this non-invasive technique will detect all sublethal embolic insults that cause significant increases in PAP. When Q does decrease with large embolic loads or impaired cardiovascular reserve, capnography, oximetry and arterial pressure monitoring may all be valuable (Table 3); however, PAP monitoring appears to be the most sensitive of these methods, detecting less catastrophic fat and marrow microembolism.

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Use of Esmolol During Anesthesia to Treat Tachycardia and Hypertension

Martin I. Gold, MD, David J. Sacks, MD, David B. Grosnoff, MD, Claire Herrington, RN, and Carmela A. Skillman, PhD

GOLD MI, SACKS DJ, GROSNOFF DB, HERRINGTON C, SKILLMAN CA. Use of esmolol during anesthesia to treat tachycardia and hypertension, Anesth Analg 1989;68:101–4.

We evaluated the clinical effectiveness of esmolol, an ultra-short-acting, cardioselective beta-adrenergic receptor blocker, in controlling sinus tachycardia and increased systolic blood pressure occurring perioperatively in 30 ASA physical status II or III patients having elective, non-cardiac surgery. Esmolol 80 mg I.V. bolus (N = 15) or placebo (N = 15) followed by 12 mg/min or placebo were infused in 30 isoflurane-anesthetized patients using a randomized double-blind study design. The bolus plus infusions were given when surgical stimuli caused heart rate to exceed 95 bpm or systolic blood pressure 140 mm Hg. Esmolol significantly decreased heart rate (107 ± 4, mean ± SEM to 99 ± 4, mean ± SEM bpm) within 45 sec after starting the bolus plus infusion; the placebo had no effect, heart rate being 105 ± 4 before and 106 ± 3 bpm after the bolus plus infusion. Patients given esmolol continued to have heart rates significantly lower than patients given placebo injections throughout a six min infusion (Ex., at 5 min 81 ± 3 vs 91 ± 4 bpm). The study demonstrated no apparent effect of esmolol on blood pressure but that esmolol is effective in treating perioperative sinus tachycardia.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

Rapid and dramatic hemodynamic changes, which may adversely affect the patient, may occur during the perioperative period (1–3). Perioperative myocardial ischemia is related to the occurrence of postoperative myocardial infarction, and ischemia is, in turn, related to tachycardia during coronary artery by-pass operations (4). Available beta-adrenergic receptor blocking agents may effectively blunt such hemodynamic changes (5,6); however, the hemodynamic instabilities are transient in nature whereas most beta-adrenergic blocking drugs have long durations of action. This may expose the patient to prolonged undesirable effects. Shorter duration of beta-adrenergic receptor blockade might increase the margin of safety.

Esmolol is the only available ultra-short acting, cardioselective beta-adrenergic receptor blocking agent. It has a distribution half-life of two minutes and an elimination half-life of approximately nine minutes (7). It has been used for treatment of supraventricular tachycardia outside the operating room (8–10), for prevention of tachycardia and hypertension associated with surgical stimuli (11–13), and for treatment of postoperative hypertension (14). The use of Esmolol for the *treatment* of intraoperative tachycardia and hypertension has not been examined. This study was designed to determine whether esmolol given by intravenous bolus loading dose followed by intravenous infusion can be effective in treatment of intraoperative tachycardia and hypertension.

Methods

Patients considered for the study were drawn from a population of patients scheduled to undergo general anesthesia for elective noncardiac surgery. The study was approved by the Human Studies Subcommittee at the Veterans Administration Medical Center in Miami, Florida. Written informed consent was obtained from all patients. Patients with A-V conduc-

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Address correspondence to Dr. Gold: Veterans Administration Medical Center, 1201 Northwest 16th Street, Miami, FL 33125.

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tion block greater than first degree, congestive heart failure, cardiac arrhythmias, or severe bronchial asthma were excluded. Some patients did have hypertension and none were receiving beta-adrenergic blocking agents prior to the study.

Preanesthetic medication consisted of 3.8 ± 0.4 mg midazolam, meperidine 1.0 ± 0.05 mg/kg, and 0.2 mg glycopyrrolate. Anesthesia was induced with 4.9 ± 3.2 mg/kg thiopental intravenously. Tracheal intubation was performed following muscle paralysis with 1.4 ± 0.1 mg/kg succinylcholine intravenously. After intubation, anesthesia was maintained with 0.6 ± 0.1% isoflurane and nitrous oxide:oxygen (3:2 lpm). End tidal carbon dioxide ranged between 35–40 mm Hg and end tidal isoflurane and nitrous oxide averaged 1 MAC as measured by scanning mass spectrometry. Vecuronium (6–10 mg) was administered intravenously if muscle paralysis was needed after intubation. Twenty-three patients required vecuronium (placebo = 12, esmolol = 11) during the operative period. Three patients (placebo = 1, esmolol = 2) had succinylcholine infusions during the surgical procedure.

Heart rate (HR) derived from the RR interval as measured by a continuously running EKG and blood pressure data as obtained by an automatic blood pressure cuff were collected. Lead V_5 of the EKG was used. HR and blood pressure were measured every min for three minutes prior to beginning administration of esmolol or placebo (control). During the infusion, HR was recorded every 15 seconds and blood pressure every minute. Blood pressure and HR were recorded every five min for 30 minutes after discontinuation of infusions.

Infusions of esmolol or placebo were initiated when HR exceeded 95 beats per min or systolic blood pressure (SBP) was greater than 140 mm Hg at any point during anesthesia after induction. The objective of the bolus plus infusion was to decrease HR or SBP at least 15% below the measured HR or BP prior to the injection of bolus. The infusion was then continued as needed to treat the sinus tachycardia or hypertension. Infusions were, therefore, longer in some patients than in others; however, the minimum duration of infusion was 6 minutes. Nonresponders were given a 6-minute period and were then "bailed out" if a clinical situation developed and continued such as severe hypertension (180 mm Hg) or severe sinus tachycardia (140 bpm). The treatment consisted of deeper inhalation anesthesia and/or fentanyl injection intravenously.

The study drug was prepared according to the manufacturer's directions: 10 ml of the commercial esmolol solution (2500 mg) were mixed with 240 ml of dextrose 5% in USP water for injection, the final esmolol concentration being 10 mg/ml. The loading dose was administered over 15 seconds and the infusion was started immediately afterwards. All solutions were used within 24 hours of mixing. The rate of esmolol infusion was 12 mg/min preceded by a loading dose of 80 mg. The corresponding volume of placebo solution was infused in control patients. The dose used in this double-blind study was determined in a preliminary open-label, randomized-controlled clinical trial (15).

Data are expressed as mean ± SEM. Comparisons were made between treatment groups based on the percent change of HR or blood pressure from control (HR or SBP immediately prior to the injection of the bolus plus infusion) using two-sided *T*-tests. Survival analyses were used to compare treatment groups with respect to the time required to reach a 15% decrease in HR or SBP. The level of statistical significance was $P < 0.05$.

Results

The average age of the patients in the esmolol group was 50 ± 4 years; the average age for the patients in the placebo group was 59 ± 2 years. All of the patients were male. Patients in the esmolol group had an average weight of 75 ± 5 kg compared to an average weight of 67 ± 3 kg for the patients in the placebo group. Patients were all ASA physical status II and III. Among the types of surgery were: exploratory laporatomy, cholecystectomy, colectomy, inguinal herniorraphy, nasal reconstruction, mastoidectomy, orchiectomy, various oral surgical procedures and panendoscopy with biopsy.

The average time of infusion in the esmolol group was 9.0 ± 1.2 min. The average infusion time in the placebo group was 8.6 ± 1.1 min. There were no significant differences in demographic data between the two groups. Further, no intervention was taken as a "bail-out" for nonresponders. Conjecture is that as time elapsed the stimulus which created the tachycardia and/or hypertension diminished and/or the anesthesia was becoming more effective.

The esmolol-treated patients had a 7.7 ± 1.3% decrease in HR within 45 sec of starting the bolus plus infusion. This was significantly greater than the 1.2 ± 1.3% decrease in HR seen in the placebo group. At 75 seconds, there was a 16.6 ± 1.7% decrease in HR (to 89 ± 3 from 107 ± 4 bpm) in the esmolol group, significantly greater than the 3.0 ± 1.3% decrease in HR (102 ± 4 from 105 ± 4 bpm) in the placebo treated group. Patients in the esmolol group maintained a

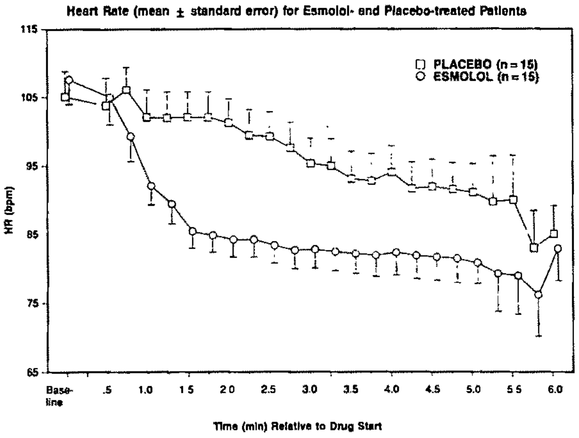

Figure 1. Heart rate in beats per minute ± SE during study drug infusion. Esmolol group compared to placebo had significantly lower heart rates from 45 seconds after start of drug infusion until discontinuation of the infusion.

Table 1. Surgical-Anesthetic Stimuli That Caused Tachycardia

Stimulus	Esmolol	Placebo
Endoscopy—Biopsy	5	2
Induction followed by intubation	8	10
Surgery: Incision or peritoneal stimulation	2	3

20–24% decrease in HR throughout the infusion, also significantly greater than in the placebo group with only a 3–13% decrease in HR during this time. Figure 1 shows the HR data for both groups. As patients recovered from the surgical stimuli, mean HR in the placebo group also decreased, but esmolol reduced the HR more rapidly. The esmolol treated group, N = 14, reached a 15% decrease in HR significantly faster than the placebo treated group, N = 14 ($p < 0.05$). Table 1 is a summation of the surgical-anesthetic stimuli causing tachycardia (or hypertension) among the 30 patients. Patients in both esmolol and placebo groups were receiving N_2O-O_2—Isoflurane at MAC + 10% on the average (both groups) as measured by the mass spectrometer.

There were no significant differences between treatment groups in the changes in blood pressure (Table 2). In fact, there were no differences in the time needed to achieve a 15% decrease in blood pressure. Further, 9 of the esmolol group and 14 of the placebo group had a 15% decrease ($p > 0.05$).

Adverse events such as severe bradycardia or hypotension, cardiac depression precipitating congestive heart failure, and increased airway resistance or bronchospasm, which may be encountered with beta-adrenergic blocking agents, were not evident in any of the study patients.

Discussion

Tachycardia associated with anesthesia and surgery, although usually short-lived, may lead to serious complications (1–3). Preventive therapy is optimal, but there are instances in which it may be clinically necessary to treat the patient after the tachycardia appears. Esmolol provides a convenient and effective treatment of these often brief episodes of tachycardia and alleviates the hemodynamic consequences of surgical stimuli (7). In this study, esmolol was effective in controlling the tachycardia due to stimuli that occurred in patients under anesthesia.

Although every patient had a six min infusion time, some patients were infused longer. There was no significant difference between the average infusion time for esmolol patients (9 min) and for placebo patients (8.6 minutes). A "bail out" plan for nonresponders existed but it was not used because of the gradual decrease in HR and SBP over time. In all probability the original stimulation and subsequent catecholamine surge decreased, or anesthesia (although at a constant end tidal concentration) was becoming more effective. Therefore, over the average infusion time of 8.6–9 minutes it appears that there is no *clinical* difference despite therapy with esmolol. However, the group receiving esmolol had a definite pharmacological effect and a significantly lower HR (20–24%) when compared to control; not so for placebo patients with an average decrease of 3–13%. For this reason esmolol given by bolus followed by infusion is useful therapeutically.

Intravenous esmolol has been shown to be effective in controlling blood pressure perioperatively in previous studies (14,16,17). The dose of E infusion used in previous studies was 300 $mcg \cdot kg^{-1} \cdot min^{-1}$, i.e. 22.5 mg/min in a 75-kg man (the average weight of the patients in the esmolol group). The blood pressure lowering effect at this higher dose was not seen until 5 to 8 minutes into the infusion. In the present study an infusion dose of 12 mg/min was used with an average infusion time of 8 to 9 minutes. It appears that a dose higher than that used in this study would be needed to control increases in blood pressure during anesthesia.

This study differed from most other esmolol investigations during anesthesia and surgery in that esmolol was given therapeutically, not prophylactically. We waited for a sinus tachycardia to occur, then we prepared the solution rapidly, withdrew 80 mg, injected a bolus load and followed with a gravity drip infusion. The pediatric infusion set allowed precise intravenous rates in 15–30 seconds. The latter was chosen because we wanted to avoid the delay asso-

Table 2. Blood Pressure Data During Study Drug Infusion and Postinfusion

	Esmolol		Placebo	
	SBP	DBP	SBP	DBP
Time (min)				
0	150 ± 8	98 ± 6	168 ± 8	109 ± 4
1.0	147 ± 8	94 ± 5	164 ± 8	102 ± 3
2.0	142 ± 6	88 ± 4	158 ± 8	100 ± 5
3.0	136 ± 5	88 ± 3	156 ± 7	95 ± 4
4.0	132 ± 5	84 ± 3	140 ± 6	88 ± 4
5.0	127 ± 5	81 ± 4	142 ± 7	89 ± 3
6.0	118 ± 8	77 ± 7	138 ± 8	91 ± 5
Postinfusion Time (min)				
5.0	117 ± 6	76 ± 5	138 ± 10	88 ± 6
10.0	122 ± 4	79 ± 4	133 ± 10	83 ± 5
15.0	120 ± 4	78 ± 4	132 ± 8	84 ± 3
20.0	128 ± 5	80 ± 4	131 ± 6	85 ± 4
25.0	127 ± 5	78 ± 5	145 ± 9	93 ± 6
30.0	124 ± 5	79 ± 6	130 ± 5	80 ± 4

Data are reported in mm Hg ± SE.
SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

ciated with the procurring and preparation for use of an infusion pump. We were able to prepare the bolus and start the infusion in less than 1 min.

Esmolol at an i.v. dose of 80 mg followed by 12 mg/min infusion was effective in the immediate treatment of tachycardia associated with anesthesia and surgery. We did not encounter hypotension, bradycardia or bronchospasm. Esmolol was easily administered by a loading dose followed by a gravity infusion. This dose was not effective in lowering blood pressure.

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Control of Intraoperative Hypertension with Isoflurane in Patients with Coronary Artery Disease:

Effects on Regional Myocardial Blood Flow and Metabolism

Lars Sahlman, MD, Italo Milocco, MD, Lennart Appelgren, MD, Göran William-Olsson, MD, and Sven-Erik Ricksten, MD, PhD

SAHLMAN L, MILOCCO I, APPELGREN L, WILLIAM-OLSSON G, RICKSTEN S-E. Control of intraoperative hypertension with isoflurane in patients with coronary artery disease: effects on regional myocardial blood flow and metabolism. Anesth Analg 1989;68:105–11.

The effect of isoflurane on regional myocardial metabolism and blood flow, when used as an adjunct to fentanyl-nitrous oxide anesthesia, to control intraoperative hypertension was investigated. Twenty-two patients with two- or three-vessel coronary artery disease with an ejection fraction >0.5 and on beta-blockers up to the morning of surgery were studied during elective coronary artery by-pass grafting. Systemic and pulmonary hemodynamics, and regional (great cardiac vein, GCVF) myocardial blood flow and myocardial metabolic parameters were measured. In 10 patients, both GCVF and global (coronary sinus, CSF) myocardial blood flows were recorded. Measurements were made 1) after induction of anesthesia but prior to skin incision, 2) during sternotomy, and 3) during isoflurane administration after its use to reduce arterial pressure to the presternotomy level. The increase in systemic arterial pressure during sternotomy was due to an increase in systemic vascular resistance accompanied by increases in heart rate, pulmonary capillary wedge pressure, (PCWP) regional myocardial oxygen consumption and extraction, GCVF and total coronary vascular resistance. Isoflurane reduced systemic arterial pressure but not PCWP, to presternotomy levels within 6.9 ± 0.7 minutes at an end-tidal concentration of 1.5 ± 0.2%. Isoflurane induced a pronounced systemic and coronary vasodilatation and increases in cardiac index, heart rate and regional myocardial oxygen extraction while the GCVF/CSF ratio remained unchanged. While mean regional—MLE% values were not effected by sternotomy, in two patients myocardial lactate production was seen during sternotomy but not during isoflurane. In another two patients, isoflurane induced lactate production. The two latter patients differed from the group as a whole mainly because of their higher heart rates during isoflurane. We conclude that isoflurane may induce myocardial ischemia even in the abscence of hypotension. This in turn may be caused by an isoflurane-induced reflex tachycardia and not necessarily redistribution of coronary flow. On the other hand, isoflurane may also have beneficial effects on stress-induced myocardial ischemia.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHESIA—cardiovascular. HEART, blood flow—myocardial.

Isoflurane, as an adjunct to fentanyl-nitrous oxide anesthesia, may favorably affect central hemodynamics when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery (1). Under these conditions, the isoflurane-induced reduction of arterial blood pressure is accompanied by a decrease in systemic vascular resistance and an increase in myocardial performance without electrocardiographic evidence of myocardial ischemia. Furthermore, it has recently been shown that low concentrations of isoflurane plus nitrous oxide may protect against pacing-induced myocardial ischemia in patients with coronary artery disease (CAD) (2). The threshold pacing rate at which first

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Address correspondence to Dr. Ricksten, Department of Anesthesia and Intensive Care, Sahlgren's Hospital, S-413 45 Gothenburg, Sweden.

signs of ischemia appear (as judged from changes in ECG or pulmonary capillary wedge pressure) is significantly higher during isoflurane anesthesia, compared to the conscious control situation.

There are, however, reports that induction of anesthesia with isoflurane alone or in combination with nitrous oxide may cause electrocardiographic and/or metabolic evidence of myocardial ischemia in patients with CAD (3–7). This has been attributed to a redistribution of coronary blood flow, coronary steal, coronary vasodilation, or to "isoflurane-induced" hypotension in combination with tachycardia (8–11).

Most of the clinical reports demonstrating that isoflurane may induce myocardial ischemia have been performed during induction of anesthesia prior to surgery and are associated with a pronounced reduction in systemic arterial pressure. Therefore, the aim of the present investigation was to study regional, myocardial circulatory and metabolic effects of isoflurane as an adjunct to fentanyl-nitrous oxide anesthesic when used to normalize intraoperative arterial hypertension back to the presurgical level.

Materials and Methods

Twenty-two patients, with a mean age of 59.1 years (range 43–69), scheduled for elective coronary artery by-pass grafting, were included in the study after informed consent was obtained. The study was approved by the Human Ethical Committee of the University of Gothenburg. All patients had two or three vessel coronary artery disease, with an ejection fraction >0.5. All patients were being treated with beta-adrenergic receptor blockers with preoperative cardiac medication, including beta-blockers, continued until the morning of surgery.

Premedication consisted of morphine 0.1 mg/kg i.m. and scopolamine 0.4 mg. Anesthesia was induced with thiopental 3–5 mg/kg, followed by pancuronium 0.1 mg/kg. Fentanyl was given in incremental doses during induction of anesthesia and after intubation, i.e. prior to the first hemodynamic measurement, up to a total amount of 10 μg/kg. Thereafter no central nervous system depressants were given until the time isoflurane was administered. The patients were normoventilated with 50% nitrous oxide in oxygen during the course of the study.

A pulmonary artery catheter (via the right subclavian vein) and a radial artery catheter were inserted for continuous recording of pulmonary and systemic arterial pressure. A coronary sinus catheter with two thermistors (n = 12) were inserted via the right internal jugular vein, using the Seldinger technique, under fluoroscopic guidance and continuous pressure monitoring. The mixing thermistor was placed in the great cardiac vein. A three thermistor Pepine regional coronary sinus catheter (n = 10) was placed, as described above, with its distal mixing thermistor in the great cardiac vein and its proximal mixing thermistor in the common coronary sinus approximately 2 cm from the coronary sinus ostium (4). The appropriate position of the coronary sinus catheter was confirmed by injection of 3–4 ml of contrast medium and by rapid central venous injection of cold saline during continuous flow recording.

Blood was sampled from the great cardiac vein (GCV) and great cardiac vein flow (GCVF) was determined in all patients. In ten patients both GCVF and coronary sinus flow (CSF) were determined.

Measurements and calculations

Systolic (SAP), diastolic (DAP) and mean arterial pressures (MAP) were measured throughout the study together with pulmonary arterial (PAP), pulmonary capillary wedge (PCWP) and right atrial (RAP) pressures. ECG, lead V_5, was continuously monitored and recorded, together with systemic and pulmonary pressures, on a Mingograph 82 (Siemens-Elema, Sweden). Blood samples for lactate and O_2-content measurements were drawn simultaneously from the GCV and systemic arteries. Blood oxygen saturation was determined using a photometric method (OSM 2 Hemoximeter, Radiometer, Copenhagen) and lactate concentration was asssayed using an enzymatic method (Lactate Analyzer 640, Roche Bio-Electronics, Switzerland). Cardiac output (CO, l/min) was determined in duplicate by the thermodilution technique. Great cardiac venous flow and total coronary sinus flow were determined by the retrograde thermodilution technique originally described by Ganz et al (12) and modified by Pepine et al (13). Normal saline at room temperature was used as the indication and injected at 40 ml/min over approximately 20 sec for each measurement. Changes in thermistor resistances due to temperature changes were measured with a Wheatstone bridge and were recorded on a Mingograph 82. Blood withdrawn via the catheter represents left anterior descending artery perfusion, which is drained by the great cardiac vein.

Cardiac index (CI, l/min/m^2), stroke volume index (SVI, ml/m^2), systemic (SVR) and pulmonary vascular (PVR) resistance mm Hg × min × m^2/l, regional (great cardial vein) myocardial oxygen consumption (regional-MVO_2, ml/min) and extraction (regional O_2 extr, %) and regional myocardial lactate extraction

Table 1. Systemic and Pulmonary Hemodynamic Data after Induction of Anesthesia but before Incision, after Sternotomy, and after Addition of Isoflurane

	Pre-incision	Sternotomy	Isoflurane
SAP mmHg	113.8 ± 2.8	175.1 ± 4.2**	113.3 ± 2.8++
MAP mmHg	80.9 ± 3.1	123.0 ± 4.3**	81.7 ± 3.2++
DAP mmHg	60.7 ± 2.6	92.7 ± 3.2**	62.3 ± 2.2++
MPAP mmHg	15.7 ± 0.9	20.8 ± 1.1**	21.0 ± 1.3$$
PCWP mmHg	9.6 ± 0.7	14.2 ± 1.0**	13.1 ± 1.1$$
RAP mmHg	6.1 ± 0.6	7.4 ± 0.7*	7.4 ± 0.9$
CI 1/min × m2	1.9 ± 0.1	2.0 ± 0.1	2.4 ± 0.1++$$
HR bpm	52.0 ± 1.5	55.3 ± 1.5*	61.9 ± 1.8++$$
SVI ml/m2	36.9 ± 2.0	36.7 ± 2.1	38.7 ± 2.1
SVR mmHg × min × $m^{2/}1$	41.4 ± 2.6	60.5 ± 3.6**	32.5 ± 1.8++$$
PVR mmHg × min × $m^2/_1$	3.4 ± 0.1	3.4 ± 0.3	3.4 ± 0.3

Pre-incision vs sternotomy *$p < 0.05$; **$p < 0.01$;
sternotomy vs isoflurane +$p < 0.05$; ++$p < 0.01$;
preincision vs isoflurane $p < 0.05$ preceded by $; $$p < 0.01.

Table 2 Coronary Hemodynamics and Myocardial Metabolism after Induction of Anesthesia but before Incision, after Sternotomy, and after Addition of Isoflurane

	Preincision	Sternotomy	Isoflurane
CPP mm Hg	51.0 ± 2.4	78.5 ± 3.3**	49.1 ± 2.0++
CSF ml/min	107.9 ± 9.3	116.3 ± 6.5	134.2 ± 11.8
GCVF ml/min	55.1 ± 4.4	73.7 ± 6.4**	76.8 ± 5.4$$
GCVF/CSF	0.50 ± 0.06	0.61 ± 0.05*	0.63 ± 0.07$
CSVR mmHg × min/ml	0.50 ± 0.05	0.70 ± 0.06**	0.38 ± 0.03++$
GCVVR mmHG × min/ml	1.09 ± 0.12	1.23 ± 0.11	0.71 ± 0.07++$$
Regional-O_2 extr. %	61.2 ± 1.8	67.0 ± 1.5**	45.5 ± 2.8++$$
Regional-MVO_2 (ml/min)	5.7 ± 0.5	8.2 ± 0.7**	5.9 ± 0.5++
Regional-MLE%	14.0 ± 2.0	18.2 ± 3.7	14.2 ± 2.4

Pre-incision vs sternotomy *$p < 0.05$; **$p < 0.01$;
sternotomy vs isoflurane +$P < 0.05$; ++$p < 0.01$;
pre-incision vs isoflurane $p < 0.05$ preceded by $; $$p < 0.01.

(regional-MLE, %) were calculated using standard formulae.

Coronary perfusion pressure (CPP, mm Hg) was defined as DAP minus PCWP. Global and regional coronary vascular resistances were defined as CPP divided by CSF and GCVF, respectively (CSVR, GCVVR, mm Hg × min/ml). In patients in whom both GCVF and CSF were measured, the GCVF/CSF ratio was determined.

Hemodynamic measurements were performed and blood samples were obtained after induction of anesthesia and tracheal intubation but prior to skin incision (presternotomy), during sternotomy and finally during addition of isoflurane in concentrations adequate to decrease MAP to presternotomy levels. Inspiratory and end-tidal concentrations of isoflurane were monitored using a Siemens-Elema, Servo gas analyzer. Regional myocardial ischemia was defined as regional myocardial lactate production and/or ST-segment changes of >0.1 mV.

All results are reported as mean ± SEM. Data were analyzed using a one way ANOVA for repeated measurements followed by Newman-Keuls multiple range test for intragroup comparisons.

Results

Data on systemic and pulmonary hemodynamics are shown in Table 1 and data on coronary hemodynamics and metabolism are shown in Table 2. Individual data on regional myocardial lactate extraction are presented in Table 3.

Sternotomy induced a 54% increase in MAP due to a 46% increase in SVR, without change in CI and SVI. Heart rate increased slightly, but significantly during sternotomy. Furthermore, PCWP and RAP increased significantly, while PVR was not affected by the sternotomy. Regional-MVO_2 increased 44% during sternotomy, accompanied by an increase in both GCVF and regional O_2-extraction. CSF did not change significantly during the surgical stress, while the GCVF/CSF ratio increased significantly. In addition, sternotomy was associated with an increase in

Table 3. Individual Data on Regional Myocardial Lactate Extraction (%)

Patient number	Preincision	Sternotomy	Isoflurane
1	7.7	24.2	15.6
2	0	29.2	19.6
3	2.8	−33.3	7.1
4	18.0	12.5	7.0
5	14.9	28.6	13.2
6	12.2	17.7	9.5
7	1.6	13.3	1.4
8	27.8	21.3	10.8
9	13.4	12.6	14.0
10	4.6	14.8	19.4
11	21.9	26.8	−2.3
12	25.0	30.4	20.7
13	15.0	24.7	23.5
14	1.8	0	−6.3
15	27.5	36.2	32.3
16	33.3	47.2	41.6
17	8.8	12.4	12.2
18	6.8	−14.6	7.7
19	23.6	27.7	17.4
20	8.1	34.5	23.3
21	14.6	18.4	22.5
22	17.7	15.9	2.4

total coronary vascular resistance (CSVR) while regional vascular resistance (GCVVR) was unchanged.

Mean values of regional-MLE % were not affected by sternotomy. In two patients (3 and 18), however, surgical stress induced regional myocardial lactate production with regional-MLE % values of −33.3 and −14.6 respectively (Table 3). Regional myocardial ischemia in these two patients was not associated with ST-segment depression or any obvious hemodynamic abberation except for an abnormal increase in PCWP (15 to 25 mm Hg) in one of the patients (18). Furthermore, in one patient (14) regional-MLE % decreased from 1.75 prior to surgical incision to 0% during sternotomy. No hemodynamic abberation or ischemic ST-segment changes were seen during sternotomy in this patient.

Reduction of systemic arterial pressure with isoflurane was achieved at an end tidal concentration of 1.5 ± 0.2% after 8.9 ± 0.7 minutes. The restoration of arterial blood pressure to the presternotomy level by isoflurane was accompanied by an increase in CI, a further increase in HR, an almost 50% decrease in SVR and no change in SVI, PVR or PCWP. Regional-MVO_2 decreased to the presternotomy level. Both GCVF and CSF were well maintained despite a fall in CPP. Thus, both CSVR and GCVVR decreased during isoflurane administration. When compared to the presternotomy values, CI, heart rate and PCWP was higher, SVR lower, while SVI and CPP was unchanged. GCVF, GCVF/CSF ratio, but not CSF was higher, while CSVR, GCVVR and regional-O_2 extraction were lower compared to the presternotomy values.

Mean regional-MLE % was not affected by isoflurane administration. The two patients (3 and 18) who developed regional myocardial ischemia during sternotomy (lactate production) did not produce lactate (regional MLE % was 7.1 and 7.7, respectively) when arterial blood pressure was normalized with isoflurane (Table 3). However, two patients (11 and 14) developed regional myocardial lactate production during isoflurane administration. In one of the patients regional-MLE decreased from 26.8 during sternotomy to −2.3 after addition of isoflurane, similar values in the second patient being 0 and −6.3. The latter two patients differed from the group hemodynamically, as they had the highest heart rate values during isoflurane administration (72 and 84 beats/min, respectively). This was probably not caused by an inadequate preoperative treatment with beta-blockers, as their heart rate responses to sternotomy did not differ from the group. The second patient also had the lowest value of CPP and developed ST-segment depression (>0.1 mV) during isoflurane administration.

Discussion

Isoflurane was used in the present study as an adjunct to fentanyl-nitrous oxide anesthesia to control intraoperative hypertension in patients with coronary artery disease. The blood pressure reducing effect of isoflurane was caused by a pronounced decrease in systemic vascular resistance, accompanied by an increase in cardiac index and heart rate while stroke volume index was unchanged. Pulmonary capillary wedge pressure increased during sternotomy but was not reduced to presternotomy values by isoflurane. These results agree with those reported by Hess et al. (1) and by O'Young et al. (14), both of whom used approximately the same protocol except that in their studies isoflurane did not increase heart rate. Furthermore, the increased pulmonary capillary wedge pressure that was associated with the stress induced hypertension was reduced with isoflurane in their studies. The differences between these results and ours can probably be explained by the fact that we used higher concentrations of isoflurane to normalize higher arterial blood pressures during sternotomy.

During sternotomy, there was a significant increase in regional myocardial oxygen extraction, indicating that great cardiac vein flow, although elevated, did not meet the increased metabolic demand. This could possibly be explained by a stress-induced sympathetically mediated increase of the coronary vascular tone as demonstrated by the 40% increase in total coronary vascular resistance during sternotomy. Our data on myocardial oxygen extraction agree with those reported by O'Young et al.

The isoflurane-induced blood pressure normalization was associated with a normalization of both regional myocardial oxygen consumption and coronary perfusion pressure, values which did not differ significantly from the preincision levels. Under these conditions, there was a pronounced decrease in regional myocardial oxygen extraction and 40–50% decrease in total and regional coronary vascular resistance. Thus, isoflurane, when used to treat intraoperative hypertension, avoiding hypotension, induced a clearcut coronary vasodilation in the present study. It has previously been shown that induction of anesthesia with isoflurane, in humans, with the development of arterial hypotension causes a coronary vasodilation (3–7). These results have been confirmed in the majority of animal studies (15–19), though two studies (20,21) have failed to show coronary vasodilation with isoflurane.

Recently Cason et al. (22) suggested that isoflurane-induced coronary vasodilation could be due to an indirect autoregulatory coronary vasodilation, caused by the associated systemic hypotension. They demonstrated in an animal model that isoflurane had only minimal effects on coronary vascular resistance when diastolic aortic pressure was held constant. Furthermore, isoflurane only mildly impairs coronary blood flow autoregulation (23) and coronary vascular reserve, i.e., the increment in coronary blood flow above resting level produced by a maximal vasodilating stimulus (23,24). Thus, based an animal experiments, the response of the coronary vascular bed to isoflurane remains controversial. However, in humans with coronary artery disease isoflurane appears to induce coronary vasodilation whether or not isoflurane is associated with hypotension.

In other words, the data from the present investigation clearly demonstrate that, at a comparable level of myocardial oxygen demand and systemic and coronary perfusion pressure, isoflurane has the potential for inducing a pronounced dilation of the coronary vasculature compared to the control situation. Our data are at variance with the results of O'Young et al. They found that isoflurane produced no coronary vasodilation, at equal levels of systemic arterial pressure, compared to the pre-sternotomy levels. In their study, isoflurane was used as an adjuvant to sufentanil-oxygen anesthesia, but the major difference between our study and theirs was that they used comparatively low concentrations of isoflurane: 0.75–1% inspiratory concentration (end-tidal concentration of isoflurane was not measured).

During the stress-induced arterial hypertension, two patients in the present study developed myocardial ischemia as judged by regional myocardial lactate production. When isoflurane was administered to normalize arterial blood pressure, lactate production was no longer seen in these patients. Thus, in these patients isoflurane anesthesia was beneficial for the ischemic heart. Whether this favorable effect of isoflurane on stress-induced regional myocardial ischemia was caused by a decreased regional myocardial oxygen demand or an increased supply, or both, cannot be deduced from the present study. However, these results are in agreement with the data from Tarnow et al (2) who showed that isoflurane-nitrous oxide anesthesia protects against pacing induced myocardial ischemia.

Two of our patients developed regional myocardial lactate production during isoflurane administration. Isoflurane thus may induce myocardial ischemia not only when associated with hypotension (3–7) but also when systemic arterial pressure is kept within the normotensive range, as in the present study. In the study of O'Young et al (14) none of the seven patients studied produced lactate during sternotomy or during isoflurane. The difference between their study and ours could probably be explained by a low incidence of myocardial lactate production when isoflurane is used to control intraoperative hypertension in patients with CAD (9% in the present study) and the low number of patients in their study. It has been suggested that isoflurane-induced myocardial ischemia in humans with CAD is caused by a redistribution of coronary flow, "coronary steal," in turn caused by coronary vasodilation (3–9). This has been supported by two recent studies in dogs with chronic coronary occlusion (17) or critical coronary artery stenoses (25), in which isoflurane induced "coronary steal" (17) and regional myocardial dysfunction (17,24) indicative of myocardial ischemia. However, other dog experiments (26), found that isoflurane-induced transmural coronary steal, in the presence of a critical coronary stenosis, does not necessarily induce ischemia as long as the regional myocardial oxygen supply/demand relation is not seriously affected. Furthermore, Cason et al found that in dogs with chronic occlusion of left arterior descending artery that isoflurane did not induce "coronary steal" if diastolic hypotension was avoided. Thus, results from these animal models are somewhat conflicting regarding the ability of isoflurane to induce myocardial ischemia. On the basis of the findings from previous studies (3–7) as well as from the present study, however, it appears that isoflurane anesthesia may cause myocardial ischemia in patients with CAD, whether it is associated with systemic hypotension or not.

It has been questioned whether isoflurane-induced myocardial ischemia can be explained by decreased coronary perfusion and/or increased heart rate not necessarily invoking a coronary steal mechanism (8,9,11). In the present study, isoflurane-induced reduction in blood pressure was associated with a significant increase in heart rate. In fact, the two patients who produced lactate during isoflurane had the highest heart rates, which in turn was not caused by an inadequate beta blockade. One of these patients also had the lowest coronary perfusion pressure and developed ST-segment depression during isoflurane. Isoflurane did not cause a significant change in the GCVF/CSF ratio. This indicates that treatment of intraoperative hypertension with isoflurane, at an end-tidal concentration of approximately 1.5% is not associated with myocardial redistribution of flow as far as this is expressed by the GCVF/CSF ratio. In one of the patients in whom lactate was produced during isoflurane administration, both GCVF and CSF was measured. Both during sternotomy and after the addition of isoflurane the GCVF/CSF ratio was 0.62. It is therefore likely that isoflurane-induced myocardial ischemia, defined as myocardial lactate production, was caused by the combination of decreased supply and increased demand (heart rate increase).

Isoflurane, when used to normalize high intraoperative arterial blood pressure and myocardial oxygen demand induces a pronounced systemic and coronary vasodilation accompanied by increases in cardiac index and heart rate.

Under these conditions isoflurane may elicit myocardial ischemia, especially if it is associated with an increase in heart rate. However, under these conditions isoflurane may also have beneficial effects on stress-induced myocardial ischemia, as shown by the abolition or attenuation of myocardial lactate production during sternotomy.

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Fifty-eight Years Ago In
Anesthesia & Analgesia

C. D. Leake, M-Y Chen: A preliminary note on the anesthetic properties of certain unsaturated ethers. Current Researches in Anesthesia and Analgesia: 1931;10:1–3.

This paper provides an opportunity to introduce to more modern anesthesiologists an important early contributor to our specialty. Chauncey Leake, from the Department of Pharmacology at the University of California Medical School in San Francisco, expolored, in a way no one had done since Meyer and Overton at the turn of the century, the relationship between molecular structure and anesthetic effect. After identifying aspects of molecular structure related to potency and toxicity, Leake set about synthesizing or having synthesized a number of new organic substances of potential use in clinical anesthesia. In this instance he and Chen reasoned that, in certain homologous aliphatic series of compounds, toxicity increases without a parallel increase in anesthetic activity in proportion to the number of carbon atoms in the straight carbon chain. So, too, does the boiling point. Also, anesthetic activity increases in the presence of both ether linkages and unsaturated chemical bonds. Therefore, "since diethyl ether is the most satisfactory alkyl ether for general anesthesia, and since ethylene is the most satisfactory unsaturated hydrocarbon for the purpose", they combined the chemical structures of an ether and an unsaturated bond into a new substance: $CH_2 = CH - O - CH = CH_2$, i.e., divinyl ether on Vinethene. Never more than 12 ml were initially available, but this was enough for Leake and Chen to demonstrate that it was volatile enough to provide a good vapor pressure at room temperature, that its olive oil:water partition coefficient was high, and that it produced rapid onset of non-toxic readily reversible anesthesia in mice. This was a most helpful addition to the anesthetic armamentarium of the time and soon divinyl ether was being widely used for open-drop induction of ether anesthesia, especially in children. It was rapid in onset, non-irritating, with a not unpleasant odor, and substantially safer than open-drop (spray) ethyl chloride, which was just too rapid in onset to control and too liable to produce arrhythmias. Eventually the disadvantages of divinyl ether became clear, including profuse sialorrhea, hepatic damage if given for more than the induction of anesthesia, and a tendency to predispose to ether convulsions. But before divinyl ether was finally abandoned, it provided thousands of children a less traumatic induction than straight open-drop ether for their T and As. Divinyl ether also provided the basis and stimulation for the development and evaluation of many new inhalation anesthetics based on molecular structure-action relationships—a search that still goes on.

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Metabolic Responses—($\dot{V}O_2$, $\dot{V}CO_2$ and Energy Expenditure)—Associated with Nasal Intubation of the Trachea

Argyro Fassoulaki, MD, PhD, DEAA, Maria Eforakopoulou, MD, and Miltiadis Vassiliou, MD

FASSOULAKI A, EFORAKOPOULOU M, VASSILIOU M. Metabolic responses—$\dot{V}O_2$, $\dot{V}CO_2$, and energy expenditure—associated with nasal intubation of the trachea. Anesth Analg 1989;68:112–15.

The effect of nasotracheal intubation on oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and resting energy expenditure (REE) was studied in 12 critically ill patients. All patients were given midazolam 0.3 mg/kg and etomidate 0.3 mg/kg followed by 8 mg of vecuronium to facilitate intubation. After nasotracheal intubation the patients were mechanically ventilated with an Erica Engström ventilator and connected to an Engström metabolic computer (EMC). Carbon dioxide production was measured using an infrared CO_2 analyzer. Resting energy expenditure was calculated by the EMC, which incorporated an oxygen cell for $\dot{V}O_2$ measurement. $\dot{V}O_2$, $\dot{V}CO_2$, and REE were recorded 5, 10, 15, 20, 25, and 30 minutes after intubation. High values of the above parameters were observed 5 minutes after intubation, values that gradually declined during the next 25 minutes. At 25 and 30 minutes after intubation $\dot{V}O_2$ was 25% and 27% lower ($P = 0.054$) than the $\dot{V}O_2$ at 5 minutes after intubation. Carbon dioxide production and REE were also lower 10, 15, 20, 25, and 30 minutes after intubation but were not significantly different from values obtained at 5 minutes. The increase in $\dot{V}O_2$ associated with nasotracheal intubation may be detrimental for patients already suffering from hypoxia.

Key Words: INTUBATION, TRACHEAL—metabolic responses. METABOLISM, OXYGEN CONSUMPTION, CO_2 PRODUCTION—tracheal intubation.

The cardiovascular responses to laryngoscopy and intubation of the trachea have been extensively investigated (1–3). In an attempt to attenuate such changes, particularly in patients with compromised myocardium, several techniques have been described (4–7). Metabolic responses such as oxygen consumption ($\dot{V}O_2$) and resting energy expenditure (REE) associated with laryngoscopy and intubation, though unstudied, would be of clinical significance as well. This study investigates the changes in $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), and REE after nasal intubation of the trachea in intensive care patients.

Patients and Methods

Twelve patients admitted to the intensive care unit (ICU) were studied. Their age varied between 21 and 74 years with a mean of 51.2 ± 20 years. Of the 12 patients three were admitted for respiratory failure due to near drowning, one due to sedatives overdose, one due to Guillain–Barré syndrome, two due to exacerbated chronic respiratory failure, and five were trauma cases with no head injury. Before intubation all patients were breathing oxygen with $F_{I_{O_2}}$ 0.30. Their Pa_{O_2} varied between 65 and 80 mm Hg and the Pa_{CO_2} between 36 and 45 mm Hg. Intravenous midazolam, 0.3 mg/kg, and etomidate, 0.3 mg/kg, the drugs we routinely administer whenever sedation/hypnosis is required in ICU patients before intubation, were followed by 8 mg of vecuronium to facilitate intubation of the trachea. All intubations were performed by the first author using direct laryngoscopy by the nasal route. After intubation each patient was mechanically ventilated with an Engström Erica ventilator with a tidal volume of 7 ml/kg and at a respiratory rate of 14 to 16 breaths/min. $F_{I_{O_2}}$ was 0.30.

$\dot{V}O_2$, $\dot{V}CO_2$ and REE were measured 5, 10, 15, 20, 25, and 30 minutes after intubation. Carbon dioxide production was measured with an infrared CO_2 analyzer (Engström-Eliza). Oxygen consumption was measured by means of an oxygen cell (galvanic fuel cell type) incorporated in the Engström Metabolic computer (EMC) to which the patient was also connected. Resting energy expenditure was calculated by

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Address correspondence to Dr. Fassoulaki, 57-59 Raftopoulou Street, Athens 11744, Greece.

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Table 1. $\dot{V}o_2$, $\dot{V}co_2$, and REE before and 5, 15, and 30 Minutes after the IV Administration of Etomidate or Midazolam in Patients Already Intubated and with Controlled Ventilation

	Before	5	15	30
Etomidate				
$\dot{V}o_2$ (ml/min)	293 ± 9	294 ± 11	286 ± 13	287 ± 13
$\dot{V}co_2$ (ml/min)	191 ± 6	192 ± 2	186 ± 5	185 ± 5
REE (Kcal/24h)	1789 ± 43	1808 ± 50	1742 ± 65	1751 ± 69
Midazolam				
$\dot{V}o_2$ (ml/min)	294 ± 10	290 ± 10	283 ± 11	287 ± 9
$\dot{V}co_2$ (ml/min)	205 ± 11	205 ± 12	198 ± 12	200 ± 12
REE (Kcal/24hr)	1785 ± 55	1788 ± 48	1738 ± 54	1751 ± 48

Values are mean ± SEM.

There are no statistically significant differences between preinjection and postinjection values.

the EMC with the method of indirect calorimetry (see Appendix). The error for average values of the EMC over 5 minutes is ±6% (8,9).

The possible effects of a bolus injection of etomidate and midazolam on $\dot{V}o_2$, $\dot{V}co_2$, and REE was studied in a separate group of 10 ICU patients who had muscle relaxation and were on controlled mechanical ventilation.

The $\dot{V}o_2$, $\dot{V}co_2$, and REE values measured before and after etomidate or midazolam administration were analyzed by means of analysis of variance (ANOVA). Analysis of variance and Newman–Keuls test were applied for the statistical analyses of $\dot{V}o_2$, $\dot{V}co_2$, REE, and RQ values measured over the 30-minute postintubation period. $P \leq 0.05$ was taken as indicating statistical significance.

Results

Table 1 shows that neither etomidate nor midazolam significantly changed $\dot{V}o_2$, $\dot{V}co_2$, or REE during the 30 minutes after injection. The high values of $\dot{V}o_2$ 5 minutes after nasal intubation (Table 2) gradually decreased and, 25 and 30 minutes after intubation, $\dot{V}o_2$ was lower by 25% and 27%, respectively, than it was 5 minutes after intubation. A slight but statistically significant difference between the $\dot{V}o_2$ values measured after intubation was found (ANOVA; P = 0.054; Newman–Keuls test; Q = 3.87, for Q = 4.15 a = 0.05). Carbon dioxide production and REE also decreased at 5, 10, 15, 20, 25, and 30 minutes after nasal intubation and were lower by 19% and 18% at 30 minutes, but the decreases were not statistically significant over time. During the postintubation period of 30 minutes, insignificant increases in RQ values were observed.

Discussion

High values of $\dot{V}o_2$, $\dot{V}co_2$, and REE were found 5 minutes after the nasal intubation of the trachea, values that declined gradually during the ensuing 25 minutes. Preintubation $\dot{V}o_2$, $\dot{V}co_2$, and REE values were not obtainable because for such measurements to be made intubation and connection of the patient to the Erica ventilator and to EMC is required. However, because neither etomidate nor midazolam affect the above metabolic parameters in the mechanically ventilated, critically ill patient (Table 1), such a decline can be considered as normal return of $\dot{V}o_2$, $\dot{V}co_2$, and REE to preintubation values.

Laryngoscopy and intubation are associated with cardiovascular and catecholamine changes (1–3,10, 11). In the present study we did not investigate the cardiovascular responses to tracheal intubation. In our opinion such changes may not be significant as the critically ill patient with cardiovascular and respiratory impairment most likely will have increased catecholamine levels and the associated cardiovascular changes. Nevertheless possible metabolic responses to intubation of the trachea have not been investigated so far.

Healthy subjects can cope with increases in $\dot{V}o_2$ and REE. However, such changes can be detrimental in patients with already compromised oxygen delivery to vital organs and tissues, as is often true in the critically ill patient. Impairment of blood oxygenation, compromised cardiac output, impaired microcirculation, all common in the ICU patient, will result in tissue hypoxia, which may be aggravated by increases in $\dot{V}o_2$ with resulting severe oxygen debt.

No previous studies of metabolic changes associated with intubation of the trachea are available for comparison with our results. Besides, in this study all intubations were nasal, as this route is our preference for longterm tracheal intubation in the ICU, and therefore these intubations possibly took longer than oral intubations would have. Additionally all patients studied were critically ill. The effects of intubation on arterial pressure are increased with increases in duration of laryngoscopy (12). Because the intubations performed in this study were nasal the duration of laryngoscopy may have been longer than if the intubations had been done via the oral route.

Exercise or abnormal metabolic demands are two possible factors involved in inadequate tissue oxygenation. Whether intubation of the trachea via the oral route is associated with similar metabolic changes remains unknown. Nevertheless, all published studies regarding the cardiovascular and catecholamine responses to intubation of the trachea deal

Table 2. $\dot{V}o_2$, $\dot{V}co_2$, REE, and RQ Levels 5, 10, 15, 20, 25, and 30 Minutes after Nasal Intubation of the Trachea

	5	10	15	20	25	30
$\dot{V}o_2$ (ml/min)	348.5 ± 27.9*	325.7 ± 27.6*	294.3 ± 27.9*	279.3 ± 19.9*	262.6 ± 19.6*	256 ± 18.8
$\dot{V}co_2$ (ml/min)	234.6 ± 22.1	218.5 ± 20.9	214.3 ± 18.1	201.2 ± 13.8	196.1 ± 13.6	189 ± 13.2
REE (Kcal/24h)	2049 ± 220	1997 ± 197	1921 ± 172	1843 ± 132	1701 ± 114	1680 ± 114
RQ	0.67 ± 0.027	0.67 ± 0.027	0.74 ± 0.032	0.72 ± 0.026	0.75 ± 0.030	0.75 ± 0.031

Values are mean ± SEM.
*$P = 0.054$; thus a slight but statistically significant difference exists among the $\dot{V}o_2$ values measured during the 30 minutes after tracheal intubation.

with oral intubation or do not discriminate between oral and nasal route.

We conclude that considering the slight but statistically significant differences between the $\dot{V}o_2$ values and the nonstatistically-significant differences between the REE values, the ICU patient who may be suffering, for a variety of reasons, from hypoxemia and hypoxia, as well as the patient with a compromised myocardium, should not be exposed to such increases in $\dot{V}o_2$ and REE during intubation, a routine procedure for the ICU and the operating room. Increases in $\dot{V}o_2$ by 25% or more are undesirable and may be clinically harmful for these patients. Because etomidate and midazolam do not reduce the $\dot{V}o_2$, $\dot{V}co_2$, and REE it might be preferable to intubate the ICU patient when anesthetized, especially, perhaps with narcotics (13–16). Further studies are required to determine whether or not techniques that attenuate the cardiovascular and humoral responses to laryngoscopy and intubation can also attenuate the metabolic responses to nasotracheal intubation.

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Appendix

Theory of measurement of $\dot{V}o_2$, $\dot{V}co_2$ and REE:

$$\dot{V}O_2 \text{ (oxygen uptake/min)} = FI_{O_2} \times \dot{V}I - FE_{O_2} \times \dot{V}E \qquad (1)$$

$$\dot{V}CO_2 \text{ (}CO_2\text{ elimination/min)} = FE_{CO_2} \times \dot{V}E - FI_{CO_2} \times \dot{V}I \qquad (2)$$

The N_2 rate of exchange/min is:

$$\dot{V}N_2 = FI_{N_2} \times \dot{V}I - FE_{N_2} \times \dot{V}E$$

but in steady state conditions $\dot{V}N_2 = 0$ so:

$$FI_{N_2} \times \dot{V}I = FE_{N_2} \times \dot{V}E \text{ and } \dot{V}E = \frac{FI_{N_2}}{FE_{N_2}} \dot{V}I \qquad (3)$$

Combining equations (1) and (3):

$$\dot{V}O_2 = FI_{O_2} \times \dot{V}I - FE_{O_2} \times \dot{V}I \frac{FI_{N_2}}{FE_{N_2}}$$

$$\dot{V}O_2 = \dot{V}I(FI_{O_2} - FE_{O_2} \frac{FI_{N_2}}{FE_{N_2}}) \qquad (4)$$

Combining equations (2) and (3):

$$\dot{V}CO_2 = F_{E_{CO_2}} \frac{F_{I_{N2}}}{F_{E_{N_2}}} \dot{V}I - F_{I_{CO_2}} \times \dot{V}I$$

$$\dot{V}CO_2 = \dot{V}I(F_{E_{CO_2}} \frac{F_{I_{N_2}}}{F_{E_{N_2}}} - F_{I_{CO_2}}) \qquad (5)$$

Because $F_{I_{N_2}} + F_{I_{O_2}} + F_{I_{CO_2}} = 1$ and $F_{E_{N_2}} + F_{E_{O_2}} + F_{E_{CO_2}} = 1$:

$$\frac{F_{I_{N2}}}{F_{E_{N2}}} = \frac{1 - F_{I_{O_2}} - F_{I_{CO2}}}{1 - F_{E_{O2}} - F_{E_{CO_2}}} \qquad (6)$$

Substituting equation (6) in equations (4) and (5):

$$\dot{V}O_2 = \dot{V}I \times F_{I_{O_2}} - F_{E_{O_2}} (\frac{1 - F_{I_{O2}} - F_{I_{CO2}}}{1 - F_{E_{O_2}} - F_{E_{CO2}}}) \qquad (7)$$

$$\dot{V}CO_2 = \dot{V}I \times F_{E_{CO_2}} (\frac{1 - F_{I_{O_2}} - F_{I_{CO2}}}{1 - F_{E_{O_2}} - F_{E_{CO2}}}) - F_{I_{CO_2}} \qquad (8)$$

Substituting a value of 0.0003 for $F_{I_{CO_2}}$ and

$\frac{1 - F_{IO_2} - 0.0003}{1 - F_{E_{O_2}} - F_{E_{CO_2}}}$ with K, equations (7) and (8) become:

$$\dot{V}O_2 = \dot{V}I (F_{I_{O_2}} - K \times F_{EO_2}) \qquad (9)$$

$$\dot{V}CO_2 = \dot{V}I (K \times F_{E_{CO_2}} - 0.0003) \qquad (10)$$

Because

$$RQ = \frac{\dot{V}CO_2}{\dot{V}O_2} \qquad (11)$$

Substituting with equations (9) and (10)

$$RQ = \frac{K\,F_{E_{CO_2}} - 0.0003}{F_{I_{O_2}} - K \times F_{E_{O_2}}} \qquad (12)$$

Calculation of the energy expenditure with the Metabolic Computer includes only expenditure components to nonprotein RQ. The relation of oxygen caloric value as a function of RQ for a carbohydrate/fat mixture at ATPD is: EE = $1.32\dot{V}O_2(1.23RQ + 3.81)$ Kcal/24 hours.

$\dot{V}$: gas volume/min
F: fractional mean concentration
RQ: respiratory quotient
I: inspired gas
E: expired gas
ATPD: ambient temperature pressure dry

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Clinical Pharmacology of Mivacurium Chloride (BW B1090U) in Children During Nitrous Oxide-Halothane and Nitrous Oxide-Narcotic Anesthesia

Joel B. Sarner, MD, Barbara W. Brandom, MD, Susan K. Woelfel, MD, Mai-Li Dong, MD, Michael C. Horn, MD, D. Ryan Cook, MD, Barbara F. McNulty, MPH, and Vicki J. Foster, MSPH

SARNER JB, BRANDOM BW, WOELFEL SK, DONG M-L, HORN MC, COOK DR, McNULTY BF, FOSTER VJ. Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia. Anesth Analg 1989;68:116–21.

We determined the dose-response relationships of mivacurium (BW B1090U) in children (2–10 years) during nitrous oxide-halothane anesthesia (0.8% end-tidal) and during nitrous oxide-narcotic anesthesia. Neuromuscular blockade was monitored by recording the electromyographic activity of the adductor pollicis muscle resulting from supramaximal stimulation at the ulnar nerve at 2 Hz for 2 seconds at 10-second intervals. To estimate dose-response relationships, for each anesthetic background four subgroups of nine patients received single bolus doses of 20–120 μg/kg mivacurium. The ED_{50} and ED_{95} (estimated from linear regression plots of log-dose vs. probit of effect) were 52 μg/kg and 89 μg/kg during halothane anesthesia and 62 μg/kg and 103 μg/kg during narcotic anesthesia. Nine additional patients in each anesthetic group received 250 μg/kg mivacurium. Three of the 18 patients given 250 μg/kg mivacurium developed cutaneous flushing; in one of these mean arterial pressure decreased 32% for less than 1 minute; no significant changes in heart rate occurred. With the increase in mivacurium dose from 120 μg/kg to 250 μg/kg the times to onset of 90% and maximum neuromuscular block decreased by 0.5 to 1 minute, and the times to recovery of neuromuscular transmission to 5% (T5) or 25% (T25) increased by 2–4 minutes. The recovery index (T25–75) in patients anesthetized with halothane was 4.3 ± 1.5 minute (mean ± SD); the time to complete recovery (T4:1 ≥ 0.75) was 19.8 ± 7.4 minutes.

Key Words: NEUROMUSCULAR RELAXANTS—mivacurium. ANESTHESIA—pediatric.

Mivacurium chloride (BW B1090U), a new nondepolarizing neuromuscular blocking agent with short duration of action, is metabolized by plasma cholinesterase (1–2). In adults when administered in doses less than 2 times the ED_{95} mivacurium appears to be devoid of cardiovascular effects (3–6). Larger doses may be associated with a transient decrease in blood pressure (5,6).

Succinylcholine, the only short-acting relaxant now in clinical use, may be associated with numerous undesirable side effects (e.g., masseter spasm, myoglobinuria, malignant hyperthermia, hyperkalemia, myalgias, fasciculations, and cardiac dysrhythmias), especially in children (7–13). Mivacurium may be an effective alternative to succinylcholine, with fewer side effects, in situations requiring rapid recovery from neuromuscular blockade. Therefore, we studied the neuromuscular and cardiovascular effects of mivacurium in children during nitrous oxide-oxygen-halothane and during nitrous oxide-oxygen-narcotic anesthesia.

Methods

Ninety children (ASA I-II) between 2 and 10 years of age having low-to-moderate risk elective surgical

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Address correspondence to Dr. Sarner: Department of Anesthesiology, Children's Hospital of Pittsburgh, 3705 Fifth Avenue at DeSoto Street, Pittsburgh, PA 15213-2583.

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procedures requiring tracheal intubation were studied. Their mean age was 5.2 ± 2.2 (SD) years; their mean weight was 20.7 ± 6.1 kg, their mean height was 111.8 ± 15.2 cm; and their mean body surface area was 0.76 ± 0.15 m^2. The study was approved by the Human Rights Committee of Children's Hospital of Pittsburgh; informed consent was obtained from parents. No patient had a history of abnormal response to neuromuscular blocking agents; none received aminoglycoside antibiotics or antihistamines within 48 hours of the study. Blood was drawn for measurement of pseudocholinesterase activity and dibucaine number immediately after induction of anesthesia. Patients were divided into 2 groups of 45 patients each. One group (Group H) was studied during nitrous oxide-oxygen-halothane anesthesia; the other group was studied during nitrous oxide-oxygen-narcotic anesthesia (Group N). Patients who received halothane were generally unpremedicated; one patient received oral diazepam (0.15 mg/kg). Patients in Group N were premedicated with variable combinations of oral diazepam (0.1–0.2 mg/kg), intramuscular morphine (0.1–0.2 mg/kg) and scopolamine (6 μg/kg), and rectal methohexital (20–30 mg/kg).

In patients in Group H anesthesia was induced with nitrous oxide (70%) in oxygen (30%) and halothane (3–5% inspired concentration). An intravenous catheter was inserted after induction of anesthesia, and an infusion of 5% dextrose in lactated Ringer's solution was begun. Atropine 10 μg/kg was given IV before tracheal intubation. Tracheal intubation was accomplished without the aid of neuromuscular blocking agents or intravenous or translaryngeal lidocaine. After intubation the end-tidal halothane concentration was reduced to 0.8% ± 0.05%, nitrous oxide (70%) in oxygen (30%) was continued, and fentanyl (up to 6 μg/kg) IV was given if needed. End-tidal halothane concentration was measured using an infrared gas analyzer (Puritan-Bennett 222) and remained stable between 0.75 and 0.85% for at least 10 minutes before administration of mivacurium.

In patients in Group N anesthesia was begun with nitrous oxide (70–80%) in oxygen (20–30%), an intravenous infusion of 5% dextrose in lactated Ringer's solution was established, and thiopental (4–10 mg/kg), diazepam (0.1–0.2 mg/kg), and fentanyl (2–6 μg/kg) were given as needed. Anesthesia was maintained with nitrous oxide (70%) in oxygen (30%) and fentanyl. These patients were intubated after the administration of mivacurium.

Blood pressure and heart rate were recorded by automated sphygmomanometry (Dinamap) in all patients. Normal minute ventilation and body temperature were maintained intraoperatively. The ulnar nerve was stimulated supramaximally (pulse width, 0.1 msec) using cutaneous electrodes on the forearm with train-of-four stimuli (2 Hz for 2 sec at 10-sec intervals). The compound electromyogram of the adductor pollicis muscle was recorded using a Puritan Bennett/Datex monitor. The degree of neuromuscular blockade was described as percent of control; the height of the T1 response (first train-of-four response) after mivacurium administration was compared to the height of T1 prior to the initial bolus of mivacurium.

Patients in Group H were divided into four subgroups of nine patients each. At least 5 minutes after intubation and immediately prior to mivacurium administration, baseline levels of blood pressure and heart rate were obtained. Three patients in the first subgroup of Group H received 20 μg/kg of mivacurium. Because this dose resulted in minimal neuromuscular blockade, the remaining six patients in this subgroup received 40 μg/kg mivacurium. Patients in the other three subgroups of group H received 60, 70, or 120 μg/kg mivacurium, respectively. Patients in Group N were divided into 4 subgroups of 9 patients each; they received an initial bolus of either 60, 70, 80, or 120 μg/kg of mivacurium, respectively. Each bolus dose was given in <5 seconds through a T-connector into a rapid i.v. infusion. Heart rate and blood pressure were recorded immediately before administration of mivacurium and at 1-minute intervals for 5 minutes thereafter. Patients also were observed carefully for cutaneous flushing or other physical signs possibly indicative of histamine release. After observation of the heart rate and blood pressure for 5 minutes, tracheal intubation in Group N patients was performed if adequate neuromuscular blockade was present. When blockade was less than 90% 5 minutes after the initial bolus of mivacurium, a second bolus of mivacurium was given to establish at least 95% blockade; intubation was then performed.

The dose-response relationship was examined initially with a single dose technique with doses estimated to be less than the ED_{95} for each group. Dose data for patients in each group were transformed to log-dose; neuromuscular blockade data were transformed to probits. A log-dose probit-response curve was constructed for each of the two anesthetic groups using least-squares regression. This dose-response relationship was used to estimate the ED_{95}. An additional 9 patients in each group received 250 μg/kg of mivacurium.

For the two higher doses, the times in minutes from injection of mivacurium to onset of 90% blockade and to onset of maximum neuromuscular block

Table 1. Dose-Response Relationships of Mivacurium in Different Age Groups

	CHILDREN	CHILDREN		ADULTS (3)	
	(Halothane)	(Nitrous-Narcotic)		(Nitrous-Narcotic)	
	(μg/kg)[a]	(μg/kg)[a,b]	(μg/m^2)	(μg/kg)[b]	(μg/m^2)
ED_{50}	52	62	1558	43	1752
ED_{95}	89	103	2717	70	3067
	(R = 0.85)	(R = 0.78)	(R = 0.74)	(R = 0.59)	(R = 0.56)
	(n = 31)	(n = 33)		(n = 35)[c]	

Dose response data for adults were not compared to data for children during halothane anesthesia.

No statistical differences between slopes of regression lines for other comparisons.

[a,b] Regression line intercepts statistically different from each other using two-tailed t-test.

[c] The adult dose-response relationship was recalculated to include patients receiving the estimated ED_{95} (n = 9) to allow comparison with data in children under similar conditions.

Table 2. Onset of Neuromuscular Blockade After 120 and 250 μg/kg of Mivacurium

Dose (μg/kg)	n	Time to 90% Blockade (min)	Time to Maximum Blockade (min)	Maximum Blockade (%)
Group N				
120	9	1.6 ± 0.7[a] (1.0–3.2)	2.4 ± 0.8[e] (1.2–3.7)	96.8 ± 4.2
250	9	1.1 ± 0.2[a,d] (0.7–1.3)	1.6 ± 0.4[e,f] (1.0–2.2)	100
Group H				
120	5	1.4 ± 0.2[b] (1.3–1.5)	2.1 ± 0.4[c] (1.7–3.0)	99.8 ± 0.4
250	9	0.8 ± 0.3[b,d] (0.5–1.0)	1.1 ± 0.3[c,f] (0.8–1.5)	100

All values are mean ± SD (range).

Comparison was made with unpaired two-tailed *t*-tests between different doses within a group and between different groups for the same dose.

[a–f] Groups statistically different from each other.

ade were recorded. The degree of blockade was referenced to the initial electromyogram baseline. Full spontaneous recovery, through $T4{:}1 \geq 0.75$, was observed in patients in Group H. Recovery data were referenced to the amplitude of the T1 response when T4 first equaled T1. Measured indices of spontaneous recovery of neuromuscular transmission for Group N included T5, T25, and T5–25. Full recovery was not observed in these patients after the initial bolus of mivacurium because it was not consistent with anesthetic requirements for the anticipated surgery.

The dose-response curves were subsequently recalculated for Group H and Group N to include the subgroups that received 120 μg/kg of mivacurium. New estimates of ED_{50} and ED_{95} were calculated from these linear regression equations. ED_{50} and ED_{95} for mivacurium were also calculated on a μg/m^2 basis for Group N to allow comparison with our data from adults (3). The body surface area of each child was estimated from standard nomograms of height and weight. The slope and intercept of the various regression lines were compared using unpaired *t*-tests.

All results are reported as mean ± SD. The data were analyzed using *t*-tests, and repeated measures analysis of variance where appropriate. Results were considered statistically significant when $P \leq 0.05$.

Results

The mean age, weight, height, and body surface area of the children in the two anesthetic groups were not statistically different. Three patients in Group H (120 μg/kg), one patient in Group H (70 μg/kg) and two patients in Group N (80 μg/kg) were omitted from analysis of neuromuscular effect because of abnormal or unavailable pseudocholinesterase activity or dibucaine number. One patient in Group H (120 μg/kg) had signs of direct muscle stimulation on the electromyographic tracing and one patient in Group N (80 μg/kg) received an incorrect dose of mivacurium; data from these patients were not included in calculation of the dose-response relationships.

Patients in Group H receiving 20, 40, 60, 70, and 120 μg/kg mivacurium developed maximum neuromuscular blockade of 5 ± 2.9, 17.8 ± 19.1, 60.0 ± 22.2, 71.6 ± 16.1, and 99.8 ± 0.4%, respectively. Patients in Group N receiving 60, 70, 80, and 120 μg/kg mivacurium developed maximum blockade of 53.6 ± 21.6, 55.4 ± 29.6, 75.8 ± 7.4, and 96.8 ± 4.2%, respectively. When dose-response curves were calculated using only doses of 20–80 μg/kg, the linear regression coefficients were 0.72 and 0.29 for Groups H and N, respectively. When the curves were recalculated to include the subgroups receiving 120 μg/kg the linear regression coefficients were 0.85 and 0.78, respectively (Table 1). The ED_{50} and ED_{95} of mivacurium reported from the latter curves were 52 and 89 μg/kg during nitrous oxide-oxygen-halothane anesthesia and 62 and 103 μg/kg during nitrous oxide-oxygen-narcotic anesthesia (Table 1). There was no difference in the slopes of these regression lines, but

Table 3. Recovery of Neuromuscular Transmission After 120 and 250 µg/kg Mivacurium

Mivacurium Dose (µg/kg)	T5 (min)	T25 (min)	T75 (min)	T4:1 ≥ 0.75 (min)	T25–75 (min)	T5–25 (min)
Group N						
120	4.9 ± 1.0[c] (3.3–6.0) n = 6	6.2 ± 2.0[d] (4.0–7.8) n = 3	NA	NA	NA	1.7 ± 0.6 (1.3–2.1) n = 2
250	6.8 ± 1.9[a,c] (3.7–9.3) n = 8	9.1 ± 2.6[b,d] (4.8–12.0) n = 8	NA	NA	NA	2.0 ± 1.0 (1.1–3.3) n = 8
Group H						
120	7.1 ± 3.8 (4.0–12.8) n = 5	9.7 ± 4.9 (5.5–17.7) n = 5	14.1 ± 7.0 (8.7–25.8) n = 5	17.9 ± 10.1 (10.5–35.3) n = 5	4.3 ± 2.2 (3.2–8.1) n = 5	2.6 ± 1.3 (1.5–4.9) n = 5
250	11.2 ± 3.9[a] (6.8–18.7) n = 9	13.6 ± 3.9[b] (8.8–21.3) n = 9	17.9 ± 4.8 (11.8–26.5) n = 9	21.0 ± 6.0 (15.2–31.8) n = 9	4.3 ± 1.2 (3.0–6.3) n = 9	2.3 ± 0.3 2.0–2.8 n = 9

All values are mean ± SD (range).

Comparison was made with unpaired two-tailed *t*-tests between different doses within a group and between different groups for the same dose.

[a–d]Groups statistically different from each other. There were no statistically significant differences in recovery times in Group H when the dose of mivacurium was increased from 120 to 250 µg/kg.

NA data not available.

there was a significant difference between the intercepts (*t*-test).

The onset times after single bolus injections of 120 µg/kg and 250 µg/kg mivacurium in both anesthetic groups are presented in Table 2. Complete blockade developed in 8 of 14 patients (n = 4, Group N and Group H, each) after 120 µg/kg mivacurium; complete blockade developed in all patients given 250 µg/kg. When the mivacurium dose was increased from 120 to 250 µg/kg, there was a statistically significant reduction in times to onset of 90% neuromuscular blockade and to maximum neuromuscular blockade in both anesthetic groups.

The data on spontaneous recovery of neuromuscular transmission after single bolus injections of 120 µg/kg and 250 µg/kg mivacurium in both groups are presented in Table 3. Time to 5% (T5) or 25% (T25) recovery increased by only 2–4 min as the dose was doubled in both anesthetic groups (see Figure 1 for halothane group). The T5–25 recovery index during halothane anesthesia (0.8% end-tidal concentration) was not significantly prolonged compared to nitrous oxide-narcotic anesthesia. Time to full spontaneous recovery (T4:1 ≥ 0.75) in patients anesthetized with halothane was 19.8 ± 7.4 minutes; the mean T25–75 recovery index was 4.3 ± 1.5 min.

No patient who received 120 µg/kg mivacurium had cutaneous flushing or clinically significant changes in mean arterial blood pressure or heart rate. In the 18 patients given 250 µg/kg mivacurium no significant difference was found over time in heart rate or mean arterial blood pressure (repeated measures analysis of variance) (Table 4). Three of these 18 patients (n = 1, Group N; n = 2, Group H) developed cutaneous flushing. Cardiovascular data were excluded for one of these patients because of concurrent difficulties in airway management. In the remaining two, maximum decreases in mean arterial pressure of 10% and 32% occurred 3 and 1 minutes, respectively, after mivacurium administration. These blood pressure changes spontaneously returned to baseline levels within 2 minutes. No significant changes in heart rate occurred in these two patients.

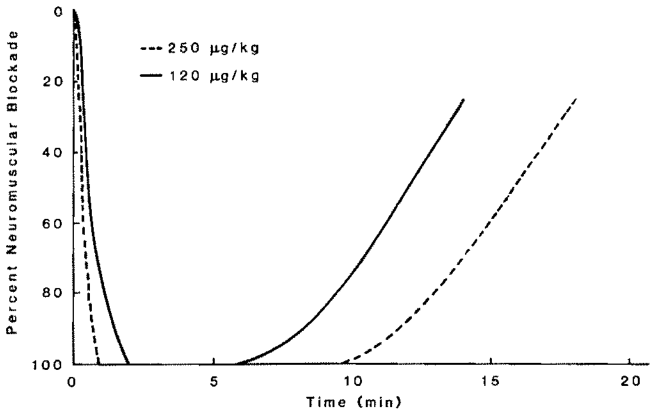

Figure 1. Schematic representation of onset and recovery profiles following bolus administration of mivacurium during halothane anesthesia in children.

Discussion

This study was designed to compare the dose-response relationships of mivacurium in children

Table 4. Effects of Mivacurium (250 μg/kg) On Blood Pressure and Heart Rate

		Times After Mivacurium Administration				
	Baseline	1 min.	2 min.	3 min.	4 min.	5 min.
Group N						
MAP (mmHg)	72.6 ± 6.0	67.2 ± 9.5	69.0 ± 6.9	67.8 ± 5.8	64.7 ± 6.3	67.7 ± 8.3
HR (beats/min)	120.6 ± 11.9	120.3 ± 7.9	120.3 ± 9.5	119.1 ± 7.6	117.1 ± 8.4	115.4 ± 7.2
Group H						
MAP (mmHg)	71.8 ± 10.6	67.9 ± 7.8	68.8 ± 8.9	69.1 ± 4.7	75.3 ± 8.5	71.1 ± 11.5
HR (beats/min)	119.9 ± 20.9	116.3 ± 20.9	115.4 ± 16.1	117.8 ± 18.4	118.8 ± 21.3	117.1 ± 21.5

All values are mean ± SD.
No statistical difference over time within groups.
n = 9 for Group N; n = 8 for Group H.

during nitrous oxide-oxygen-halothane and nitrous oxide-oxygen-narcotic anesthesia. The ED_{50} of mivacurium during halothane (0.8% end-tidal concentration) anesthesia was a significant 15% less than it was during nitrous oxide-narcotic anesthesia. Potent inhalational anesthetics are known to augment the effects of nondepolarizing neuromuscular blocking agents, and potentiation of mivacurium by isoflurane has been demonstrated in adults (3). In this study the end-tidal halothane concentration was maintained constant. The relationship between mivacurium dosage requirements and various depths of inhalational anesthesia remains to be determined.

We previously studied the effects of mivacurium in adult patients during nitrous oxide-oxygen-narcotic anesthesia (3). Compared with adults, children require significantly more mivacurium during nitrous oxide-oxygen-narcotic anesthesia on a μg/kg basis. When referenced to body surface area (i.e., $\mu g/m^2$) however, the dosage requirements are not significantly different (Table 1). This suggests that age-related dosage requirements for mivacurium may be associated with age-related differences in volume of distribution.

More rapid onset time is a recognized advantage of increasing the dose of a nondepolarizing relaxant. Times to onset of 90% blockade and to onset of maximum blockade were significantly decreased in both anesthetic groups when the mivacurium dose was increased from 120 to 250 μg/kg. Onset times were also significantly more rapid in patients anesthetized with halothane who received 250 μg/kg of mivacurium than they were in patients anesthetized with narcotics who received the same dose of mivacurium. This difference in times to onset between groups may be due to a difference in potency of mivacurium during different anesthetic backgrounds. A dose of 250 μg/kg mivacurium is 4.8 times the ED_{50} during halothane anesthesia; the same dose is 4.0 times the ED_{50} during nitrous oxide-narcotic anesthesia. Whether increasing the mivacurium dose above 250 μg/kg will further decrease onset time remains to be determined.

Spontaneous recovery from mivacurium-induced neuromuscular blockade was rapid in all patients and was not significantly prolonged during halothane anesthesia. Rapid recovery may be related to enzymatic degradation of mivacurium by plasma cholinesterase with a resultant short half-life. Previous reports (14,15) have described a method to estimate the pharmacokinetic half-life of a drug from observation of effect. Briefly, doubling the dose of drug will produce a duration of action that is prolonged by the elimination half-life of the drug. Figure 1 is a schematic representation of the neuromuscular blockade profiles associated with an approximately two-fold increase in the dose of mivacurium in our pediatric patients during halothane anesthesia. On this basis our data on recovery suggest that the plasma half-life of mivacurium is very short, on the order of several minutes. A similar in vitro half-life of mivacurium of 2.6 minutes was recently reported by Cook et al. (2).

Mivacurium has been reported to have cardiovascular effects in some patients, particularly when administered in doses exceeding two times the ED_{95} (5,6). We observed cutaneous flushing in three patients given 250 μg/kg mivacurium and a transient 32% decrease in mean arterial pressure in one of these patients. Flushing was not always associated with hypotension. When hypotension did occur it resolved rapidly and spontaneously. Neither of these side effects was observed in patients receiving lower doses of mivacurium.

In summary, mivacurium appears to be a relatively short-acting nondepolarizing muscle relaxant that has minimal cardiovascular effects when administered in doses up to and including 2.5 times the ED_{95} in children. Because of its relatively rapid onset and rapid recovery, mivacurium may offer an alternative to succinylcholine.

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Cerebral Blood Flow Does Not Change Following Sodium Nitroprusside Infusion During Hypothermic Cardiopulmonary Bypass

Anne T. Rogers, MBChB, FRCP(C), Donald S. Prough, MD, David A. Stump, PhD, Glenn P. Gravlee, MD, Kevin C. Angert, MD, Raymond C. Roy, MD, PhD, Stephen A. Mills, MDCM, and Laura Hinshelwood, MA

ROGERS AT, PROUGH DS, STUMP DA, GRAVLEE GP, ANGERT KC, ROY RC, MILLS SA, HINSHELWOOD L. Cerebral blood flow does not change following sodium nitroprusside infusion during hypothermic cardiopulmonary bypass. Anesth Analg 1989;68:122–6.

Changes in cerebral blood flow (CBF) associated with decreases in mean arterial pressure (MAP) produced by sodium nitroprusside (SNP) infusion were measured by intra-aortic injection of ^{133}*Xe in 17 patients during hypothermic cardiopulmonary bypass (CPB). In each patient, CBF was determined at baseline and then again following SNP-induced reduction of MAP. Two groups were studied. In Group I (n = 9),* $PaCO_2$ *was maintained near 42 mm Hg uncorrected for nasopharyngeal temperature (NPT). In Group II (n = 8),* $PaCO_2$ *was maintained near 60 mm Hg, uncorrected for NPT. Nasopharyngeal temperature, MAP, pump oxygenator flow,* PaO_2*, and hematocrit were maintained within a narrow range in each patient during both studies. Since the baseline CBF determinations were conducted at the higher MAP in all subjects, we corrected post-SNP CBF data for the spontaneous decline that occurs over time during CPB. In Group I, a reduction in MAP from 76 ± 9 mm Hg (mean ± SD) to 50 ± 6 mm Hg was associated with a reduction in CBF from 17 ± 5 to 13 ± 3 ml·100* $g·min^{-1}$ *(*$P < 0.01$*), a decrease that became statistically insignificant once the time correction factor had been applied (16 ± 4 ml·100* $g^{-1}·min^{-1}$*). In Group II, MAP declined from 75 ± 5 mm Hg to 54 ± 5 mm Hg, and CBF declined from 25 ± 10 to 17 ± 7 ml·100* $g·min^{-1}$ *(*$P < 0.01$*), but, again, after time correction, the CBF decline was statistically insignificant (22 ± 8 ml·100* $g^{-1}·min^{-1}$*). We conclude that SNP infusion is associated with a decrease in CBF during hypothermic nonpulsatile CPB but that the decrease is not significant when corrected for the duration of cardiopulmonary bypass.*

Key Words: BRAIN—cerebral blood flow. ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroprusside. PHARMACOLOGY—nitroprusside. ANESTHESIA—cardiovascular.

Myocardial revascularization is associated with at least a 1.0% incidence of permanent stroke (1). A much higher percentage of patients have evidence of cognitive dysfunction (2) or biochemical evidence of neural damage (3). Recently, the incidence of neurologic damage has been increasing, possibly because of an increasingly aged population undergoing this procedure (4). Despite the socioeconomic impact of these sequelae of a surgical procedure that is performed over 200,000 times per year (5), remarkably little is known about the cerebral circulation during cardiopulmonary bypass (CPB). Clinical studies have appeared only in the last few years (6–9) and have yet to define many important physiologic and pharmacologic responses, including the correct management of $PaCO_2$ during CPB. Some authorities suggest that $PaCO_2$ should be managed in the so-called "alpha-stat" manner, in which $PaCO_2$ is maintained at 40 mm Hg when measured in the blood gas machine at 37°C (approximately 27 mm Hg when corrected for a body temperature of 28°C), while others recommend the pH-stat method in which temperature-corrected

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Address correspondence to Dr. Rogers, Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, 300 South Hawthorne Road, Winston-Salem, NC 27103.

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$PaCO_2$ is maintained at 40 mm Hg (approximately 60 mm Hg at 37°C in the blood gas machine [10]).

Not only do these two different techniques produce markedly different levels of cerebral blood flow (CBF) (9), they also interact strongly with subsequent pharmacologic therapy. For instance, phenylephrine infusion does not increase CBF if the alpha-stat approach is employed, but it increases CBF substantially if the pH-stat approach is used (11).

Sodium nitroprusside (SNP) is commonly employed as an arterial vasodilator during CPB to treat arterial hypertension and prevent increased noncoronary collateral flow and dissection at the aortic cannulation site. In animal models with an intact circulation, SNP-induced hypotension causes either no change or a modest decrease in cerebral blood flow (CBF); the effects depend on whether mean arterial pressure (MAP) decreases below the lower limit of cerebral autoregulation (12,13,14,15). In anesthetized patients treated with SNP, CBF remains unchanged at levels of MAP usually associated with intact autoregulation (16,17).

Clinical studies of CBF during hypothermic CPB have produced conflicting results regarding the persistence of cerebral autoregulation. In studies employing intra-arterial ^{133}Xenon clearance, Govier et al. concluded that autoregulation remains intact, with extension of the lower limit of MAP to 30 mm Hg (7). In contrast, Lundar et al. used a transcranial Doppler estimation of middle cerebral artery velocity to demonstrate that CBF varied in a pressure-passive fashion (8). $PaCO_2$ strongly affects CBF during CPB (9), and differences in acid-base management explain the conflicting results of these investigators. Studies comparing the effect of two acid-base strategies commonly employed during CPB (11,18) on the relationship between MAP and CBF have confirmed this. If temperature-uncorrected $PaCO_2$ is maintained near 40 mm Hg (alpha-stat approach), cerebral autoregulation is preserved, while maintenance of temperature-uncorrected $PaCO_2$ near 60 mm Hg (pH-stat approach) renders CBF perfusion-pressure dependent.

The effects of SNP infusion on CBF during CPB have not been defined. We examined the response of CBF to SNP-induced reductions in MAP during hypothermic CPB for two different types of acid-base management: 1) temperature-uncorrected $PaCO_2$ = 40 mm Hg (alpha-stat), and 2) temperature-uncorrected $PaCO_2$ = 60 mm Hg (pH-stat).

Materials and Methods

We studied 17 adult patients (14 male, 3 female) with a mean age of 61 years (range, 40 to 72) undergoing coronary artery bypass grafting (CABG). No patient had clinical evidence of cerebrovascular disease or uncontrolled arterial hypertension. The Institutional Clinical Research Practices Committee approved the study and we obtained written informed consent from each subject. All patients were premedicated with oral lorazepam 0.05 $mg \cdot kg^{-1}$ and morphine sulphate 0.1 $mg \cdot kg^{-1}$ im. Fentanyl 75 $\mu g \cdot kg^{-1}$ iv induced narcosis and pancuronium 0.1 $mg \cdot kg^{-1}$ iv produced neuromuscular blockade. Following tracheal intubation the patients were ventilated with 100% oxygen. They received no additional anesthetic drugs, before or during CPB, until completion of CBF studies. Those requiring additional anesthetic drugs or pharmacologic manipulation of blood pressure or heart rate before completion of CBF measurements were not entered into the study.

CPB was conducted with a membrane oxygenator (BOS-CM50 Baxter Bentley, Irvine, CA) and nonpulsatile perfusion through an ascending aortic cannula. A non-blood priming solution was used. Central venous pressure (CVP) was maintained close to zero mm Hg by allowing unrestricted venous drainage to the reservoir of the bypass circuit. The perfusionist maintained nasopharyngeal temperature (NPT), hematocrit (Hct), PaO_2, systemic flow ($\dot{Q}$), and $PaCO_2$ within narrow limits, permitting no greater than a 3% change in controlled variables between studies in individual patients.

Subjects were randomized as follows: in Group I (n = 9), temperature-uncorrected $PaCO_2$ was maintained near 40 mm Hg by varying fresh gas flow to the membrane oxygenator; in Group II (n = 8), temperature-uncorrected $PaCO_2$ was maintained near 60 mm Hg by addition of carbon dioxide to the gas flow as required. An online $PaCO_2$ analyzer (Bentley Gas-Stat,®) continuously monitored $PaCO_2$ during CPB, and these values were confirmed by intermittent arterial blood gas sampling. We carried out a baseline CBF study after cross-clamping the aorta, when hypothermic CPB had been stable for approximately 5 minutes. MAP was then decreased at least 20% by continuous infusion of SNP. Three to four min after MAP became stable, we performed a second CBF measurement.

The CBF measurements were made in the same order in all patients, i.e., a baseline measurement at the higher MAP followed by a second measurement after SNP had lowered MAP. Since SNP has cerebrovascular effects that may persist for some time after discontinuation of infusion, we believe that randomization of the direction of MAP change would have been inappropriate for this study design. To compensate for this, the second CBF measurements were

Table 1. Variables Controlled in Evaluating Correlation between MAP and CBF (Mean ± SD)

	Group I		Group II	
	Baseline	Post-SNP	Baseline	Post-SNP
	Elapsed time = 21 ± 6 min		Elapsed time = 23 ± 9 min	
MAP (mm Hg)	76 ± 9	50 ± 6	75 ± 5	54 ± 5
NPT (°C)	27.5 ± 1.1	27.6 ± 1.2	27.3 ± 1.0	27.2 ± 0.8
Hct (%)	23.7 ± 4.4	24.0 ± 4.6	24.6 ± 3.7	25.1 ± 3.8
PaO_2 (mm Hg)	281 ± 134	282 ± 50	245 ± 32	243 ± 10
$\dot{Q}$ ($l \cdot min^{-1} \cdot m^{-2}$)	2.0 ± 0.4	2.0 ± 0.4	1.8 ± 0.2	1.8 ± 0.2
$PaCO_2$ (mm Hg)^a	42 ± 2	42 ± 2	60 ± 14	62 ± 13

MAP = mean arterial pressure; NPT = nasopharyngeal temperature; Hct = hematocrit; $\dot{Q}$ = systemic flow; a = temperature uncorrected.

corrected for the known decline in CBF occurring with time during hypothermic, nonpulsatile CPB (11). We used the following formula for time-correction of CBF data:

$$CBF_{est} = CBF_{SNP} + [CBF_b \times 0.0087 \times \text{time difference (min)}],$$

where CBF_{est} = estimated CBF; CBF_{SNP} = post-SNP CBF; CBF_b = baseline CBF; and 0.0087 = time correction coefficient.

CBF was measured in both hemispheres using a portable regional cerebral blood flow (rCBF) system developed at the Wake Forest University Medical Center (Blood flow system—Carolina Medical Electronics, King, NC). This consists of 16 solid-state cadmium telluride gamma-ray detectors mounted in a flexible helmet secured to the operating room table. Data are initially processed and displayed on a color graphic terminal mounted on a portable cart containing a microcomputer connected to detectors by a 7.62 m RS232 cable. For rapid simultaneous analysis of individual brain regions, data are transferred via modem to a central vax 730® computer (Vax Digital Equipment Corp., Maynard, MA).

During CPB, we obtained CBF measurements by injecting 3-5 mCi ^{133}Xenon (^{133}Xe) in sterile saline into the arterial line of the pump-oxygenator proximal to the filter. This method permits analysis of ^{133}Xe clearance using mathematical techniques developed for intra-arterial injection, without adding the risk of a separate arterial access site or of increased duration of surgery. Subsequent CBF measurements were made approximately 15–20 min after the initial injection. In order to eliminate artifacts due to residual xenon during repeat injections, we rejected those curves with baseline count rates exceeding 10% of the peak count rate. Additionally, for the repeat injection, we increased the dose of ^{133}Xe by 50% and consistently employed the maximum possible interstudy interval.

As suggested by Meric et al. (19), ^{133}Xe clearance curves were not corrected for extracerebral delivery and washout. Consequently, this is present as a small but consistent error in all CBF measurements (<5%). We employed the CBF-15 technique of calculation (20) after correcting for changes in the tissue-blood solubility coefficient for ^{133}Xe produced by hypothermia and hemodilution (21).

The mean global CBF ± standard deviation for each subject at each measurement interval was determined by averaging rCBF values from all 16 detector locations.

To insure comparability of controlled variables, data for NPT, Hct, PaO_2, $\dot{Q}$, and $PaCO_2$ were averaged within each group and the standard deviations of the means were calculated. Values for the independent variable MAP within each group were compared by paired two-tailed *t*-test, to insure a significant reduction ($P < 0.05$). CBF values within each group were then analyzed by paired two-tailed *t*-test to establish whether the decrease in MAP produced a significant change in CBF ($P > 0.05$).

To assure the validity of using mean CBF values for each patient, we tested the homogeneity of rCBF values. Standard deviations for each patient's mean CBF were calculated from the rCBF values at all 16 probe locations at each level of MAP. All values are expressed as mean ± standard deviation (SD).

Results

Table 1 shows values for controlled variables during baseline and repeat CBF measurements. Within groups, NPT, Hct, PaO_2, $\dot{Q}$, and $PaCO_2$ were similar at both measurement intervals. Figure 1 shows MAP and CBF data describing the response to SNP infusion before time correction. Following time-correction of the CBF data, however, we found that no significant decrease in CBF had occurred following SNP infusion (Fig. 2). Mean CBF in Group I changed from 17 ± $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 16 ± 4 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (N.S.) and in Group II it decreases from 25 ± 10 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ to 22 ± 8 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ (N.S.).

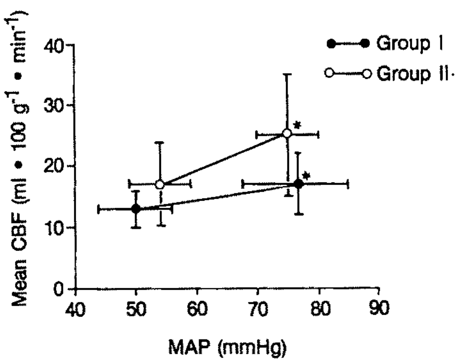

Figure 1. Mean cerebral blood flow (CBF) response to SNP-induced decreases in mean arterial pressure (MAP) in Group I ($PaCO_2$ 40 mm Hg, uncorrected for temperature) and Group II ($PaCO_2$ 60 mm Hg, uncorrected for temperature) patients. Before temperature correction, both declines were statistically significant. * = $P < 0.01$.

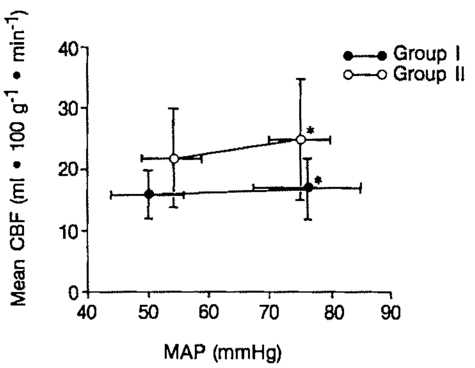

Figure 2. Mean CBF response to SNP infusion during CPB after correction for the effect of elapsed time between CBF measurements. * = no significance.

Discussion

Although several studies have reported on the relationship between MAP and cerebral blood flow during hypothermic CPB (25–30°C) over a wide range of MAP values (15–111 mm Hg) (6,7,8,11,18,22), none have specifically addressed the cerebrovascular response to sodium nitroprusside infusion. The present study looked at this relationship in order to ascertain whether cerebral blood flow changed after administration of this frequently-used vasodilator. Because $PaCO_2$ management during CPB varies among clinicians as well as among institutions, we compared the MAP/CBF response to SNP using the two standard approaches, the alpha-stat and pH-stat methods.

Recent reports have emphasized that the choice of acid-base management profoundly affects CPB's influence on cerebral autoregulation (11,18). When blood gas tensions are controlled by the alpha-stat method, autoregulation persists (11) and, in fact, the plateau is shifted leftwards down to an MAP of 15–30 mm Hg (7,18). In contrast, blood gas tension maintenance which adds CO_2 to the inflow gas (pH-stat method) causes CBF to increase in response to rising MAP (8,11,18).

We found that SNP-induced decreases in MAP were not associated with any significant change in time-corrected CBF during hypothermic, nonpulsatile CPB. This is in agreement with studies in normothermic anesthetized patients (16,17) showing stability of CBF during SNP infusion over a similar MAP range (>50 mm Hg). CBF was considerably higher in Group II patients compared to those in Group I, consistent with the differing $PaCO_2$ levels (9). However, both groups responded similarly to SNP infusion: CBF did not decrease significantly. On the basis of previous studies showing that the pH-stat method of blood gas management results in disruption of cerebral auto-regulation (8,18), we predicted that CBF would decrease in our Group II patients. One could speculate that SNP exerted a direct vasodilatory effect on the cerebral vasculature of these patients, thus offsetting the effect of decreased MAP.

It is possible, were the differences in Group II between baseline CBF and time-corrected, post-SNP CBF to be sustained in a larger series, that the decline in CBF would become significant. If so, an assessment of the accompanying cerebral metabolic response would be potentially useful in clarifying whether the decline in flow posed any significant risk of cerebral ischemia. Preliminary data suggest, however, that such a risk is unlikely, in light of the very narrow cerebral arteriovenous oxygen content difference in patients managed at levels of $PaCO_2$ similar to those employed in Group II (23).

The optimal MAP for cerebral perfusion during CPB remains controversial. Several authors have attempted to correlate MAP during CPB with neuropsychologic outcome with conflicting results (24,25,26). To date, few studies describe the relationship between CBF during CPB per se and such outcome. In 14 patients undergoing CABG, Freeman et al. examined the relationship among several demographic and intraoperative variables (27). These included age, the duration of CPB and the intraoperative level of CBF. They concluded that intraoperative CBF did not correlate with postoperative neurologic dysfunction (27). However, this series was small and must be regarded as preliminary.

Infusion of SNP for control of mean arterial pressure during hypothermic, non-pulsatile cardiopulmonary bypass is not associated with significant changes in cerebral blood flow; this holds true regardless of which type of acid-base management (alpha-stat or pH-stat) is employed.

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Is the Priming Principle Both Effective and Safe?

Peter S. A. Glass, FFA (SA), William Wilson, MD, Jennie A. Mace, MD, and Robert Wagoner

GLASS PSA, WILSON W, MACE JA, WAGONER R. Is the priming principle effective and safe? Anesth Analg 1989;68:127–34.

This study determined the priming dose of vecuronium (V), pancuronium (P) and atracurium (A) that resulted in the most rapid onset of neuromuscular blockade (NMB) in 150 patients given either V 0.08 mg/kg, P 0.1 mg/kg or A 0.6 mg/kg. Patients were further divided (n = 10 per group) to receive no prime or 5%, 10%, 15% or 20% of the total dose as a prime followed 5–7 minutes later by the remaining (intubating) dose. A further 10 patients received 0.04 mg/kg d-tubocurarine followed by 1.5 mg/kg succinylcholine (S). Priming significantly shortened the onset of NMB. The priming doses producing the most rapid onset were 0.012 mg/kg for V, 0.015 mg/kg for P and 0.09 mg/kg for A. The S resulted in significantly greater NMB at 60 sec than any priming dose of A, V or P. There was no difference between the three nondepolarizing neuromuscular blockers in shortening the onset of NMB produced by priming. To evaluate both the effect of the "optimal" priming dose in awake patients and the effect of increasing intubating doses on NMB an additional 40 patients were given V 0.012 mg/kg followed by V 0.08, 0.1, 0.12 or 0.15 mg/kg. Increasing the intubating dose did not improve onset of NMB. The "optimal" priming dose, however, resulted in a high incidence of symptoms of muscle weakness. We conclude that priming shortens the onset of NMB similarly between V, P and A but the priming dose producing the most rapid onset of NMB also results in a high incidence of side effects and therefore the priming principle should be used with caution.

Key Words: NEUROMUSCULAR RELAXANTS—atracurium, pancuronium, vecuronium, succinylcholine. PHARMACODYNAMICS—priming principle.

The priming principle, initially described in humans by Gergis (1) and by Hatton (2) and their associates, was then popularized as the "priming principle" by Schwartz et al. (3). Its underlying basis is that onset time for a nondepolarizing muscle relaxant can be shortened significantly by administration of a small sub-clinical "priming" dose several minutes prior to the injection of a larger "intubating" dose (3–5).

The most important application of the priming principle is to produce rapid onset of neuromuscular relaxation with a nondepolarizing muscle relaxant for a rapid sequence tracheal intubation (preferably comparable to that of succinylcholine) when use of succinylcholine may be contraindicated or controversial (e.g. burns, open eye, full stomach, neurological disease, etc.).

Of the currently available nondepolarizing muscle relaxants in clinical use in the United States, vecuronium, pancuronium, and atracurium are the most likely to be used for the application of the priming principle. Though several clinical studies have applied the priming principle, none have either compared these three nondepolarizing muscle relaxants to establish if there is a difference in their ability to increase the rate of onset of neuromuscular blockade when ideal priming doses are used, nor defined the clinical implications of the "optimal" priming dose.

This study was undertaken 1) to establish if priming does indeed shorten onset time; 2) to define the priming dose producing the most rapid onset of neuromuscular blockade ("optimal" priming dose) for vecuronium, pancuronium or atracurium and the "optimal" intubating dose for vecuronium; 3) to determine any difference among these three agents when used to shorten onset time when using priming doses; and, 4) to evaluate the effect of the optimal priming dose on the awake patient. We also compared the onset times to that of succinylcholine as the

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Address correspondence to Dr. Glass, Duke University Medical Center, P.O. Box 3094, Durham, NC 27707.

Table 1. Priming and Intubating Doses for Phase I

Drug	Priming Dose Mg/Kg	Intubating Dose Mg/Kg
Atracurium (Total Dose 0.6 mg/kg)	0.00	0.60
	0.03	0.57
	0.06	0.54
	0.09	0.51
	0.12	0.48
Pancuronium (Total Dose 0.1 mg/kg)	0.000	0.100
	0.005	0.095
	0.010	0.090
	0.015	0.085
	0.020	0.080
Vecuronium (Total Dose 0.08 mg/kg)	0.000	0.080
	0.004	0.076
	0.008	0.072
	0.012	0.068
	0.016	0.064
Succinylcholine	0.04 d-tubocurarine	1.5

control standard for rapid onset neuromuscular blockade.

Materials and Methods

Following Institutional Review Board approval 200 ASA physical status 1–3 patients scheduled for elective surgery gave informed consent for participation in this study. In Phase I of the study 160 patients were randomly divided into four groups depending on the muscle relaxant given, i.e., atracurium, pancuronium, vecuronium or succinylocholine. There were 10 patients in the succinylcholine group. For the three nondepolarizing muscle relaxants studied, the patients were further divided into five groups of 10 patients each according to the priming dose given. The priming dose was calculated as no prime and 5%, 10%, 15% or 20% of the total dose. The total dose of vecuronium was 0.08 mg/kg, of pancuronium 0.1 mg/kg, and of atracurium 0.6 mg/kg. Patients given succinylcholine received 0.04 mg/kg of d-tubocurarine followed by 1.5 mg/kg succinylcholine (Table 1).

Patients were premedicated with diazepam, anesthesia was induced with 1–2 μg/kg of fentanyl and thiopental 4–6 mg/kg and maintained with nitrous oxide, oxygen and additional fentanyl, up to a total of 5 μg/kg as needed. The arm free of the intravenous infusion catheter was prepared for surface electrode stimulation of the ulnar nerve and measurement of the evoked electromyographic response of the digiti minimi muscle. The forearm and hand were immobilized for recording purposes. Following induction of anesthesia, neuromuscular transmission using a Puritan Bennett NMT monitor™ (NMT) which measures the compound evoked electromyograph, was calibrated. The NMT calibrates by increasing the stimulus current by 5 mAmp increments until there is no further increase in the compound EMG. A current 20% greater than this is then utilized (i.e., a supra maximal stimulus). The resultant evoked EMG is then stored as the baseline value. The compound electromyograph of the first stimulus of each subsequent train of four is then compared to the baseline value and this ratio is then expressed as a percent (T1%). Every 20 seconds a TOF impulse is given which then yields T1%.

Following calibration of the NMT the priming dose was given. The intubating dose was always given a minimum of 5 minutes after the priming dose. If T1% was still decreasing at 5 minutes then the intubating dose was given immediately following the 3rd successive T1% reading that was within 2% of the previous T1%. The intubating dose was the total dose minus the prime dose. The time at which the intubating dose was given varied according to the time taken for the priming dose to produce a maximal effect. Sixty seconds following the intubating dose tracheal intubation was attempted. Intubating conditions were judged by a person experienced in endotracheal intubation who was blinded to the muscle relaxant and priming dose used. Intubating conditions were assessed according to the method of Twohig, Ward and Corall (6).

In Phase II of the study vecuronium was further evaluated in an additional forty patients. Specifically we studied the effect of the "optimal" priming dose on the awake patient and the effect of progressively increasing the intubating dose. All patients received the "optimal" priming dose for vecuronium established in Phase I (0.012 mg/kg). The patients were then divided into 4 groups of 10 patients each receiving either 0.08, 0.1, 0.12, or 0.15 mg/kg of vecuronium for the intubating dose.

The patients were premedicated as in Phase I but, in addition, received a small supplement of I.V. sedation (diazepam < 0.05 mg/kg) or analgesia (fentanyl < 2 μg/kg) to facilitate awake calibration of the NMT monitor. After NMT calibration, the priming dose of 0.012 mg/kg was given and neuromuscular transmission was again continuously monitored every 20 seconds. Three and a half minutes after the priming dose was given, its effect in awake patients was determined by asking the patients if they: a) experienced any diplopia; b) were able to head lift for 4 seconds; c) could take a vital capacity breath; d)

Table 2. Maximal Effect of the Priming Dose on T1% (Mean and Range)

	Priming Dose as a Percent of Total Dose				
Drug (Total Dose)	No Prime	5%	10%	15%	20%
Atracurium (0.6 mg/kg)	99.1 (95–100)	95.6 (87–100)	95.4 (87–100)	92.5 (77–100)	75.3 (50–100)
Pancuronium (0.1 mg/kg)	98.8 (94–100)	93.6 (78–100)	95.5 (89–100)	91.7 (65–100)	90.8 (75–100)
Vecuronium (0.08 mg/kg)	98.3 (95–100)	96.7 (90–100)	96.1 (79–100)	93.5 (84–100)	94.6 (83–100)
Succinylcholine (0.04 mg/kg d-tubocurarine prime + 1.5 mg/kg succinylcholine)	98.1 (83–100)				

were able to protrude their tongue, and e) were able to swallow. Four and a half minutes after the dose, a rapid sequence induction of anesthesia was performed using 3–6 mg/kg of thiopental and the randomly assigned intubating dose of vecuronium.

Sixty seconds after induction of anesthesia, tracheal intubation was attempted with intubating conditions evaluated subjectively by an individual experienced at tracheal intubation. Neuromuscular transmission was measured by continuous NMT monitoring every 20 seconds as in Phase I.

Onset of neuromuscular transmission was evaluated by 3 criteria: 1) the time course of T1% following the intubating dose at each 20 sec interval from 0–180 seconds; 2) the T1% percent after 60, 80 and 100 sec; and 3) the time for T1% to reach 20% or less.

The time to reach the maximal effect of the priming dose on T1% was determined in each group using only data from patients in whom a change in T1% was seen.

The "optimal" priming dose was taken as the dose that resulted in the shortest time for onset of neuromuscular blockade, the lowest T1% at 60 sec and the earliest time to T1% < 20% (after the intubating dose), yet showed the least change in T1% following the priming dose.

Statistical analysis of the effects of different nondepolarizing muscle relaxants and priming doses on the overall time course of neuromuscular depression was by repeated-measures analysis of variance (BMDP program P2V). The main factors in the model were the drug given and the amount of the priming dose, while the measurements of T1% from 0 to 180 sec were treated as a repeated measure (time factor). Analysis of the time taken for the priming dose to produce maximal depression of T1% was by two-way ANOVA (BMDP program P2V) with drug and priming dose as the main factors. Analysis of the degree of neuromuscular depression 60, 80, and 100 seconds after intubation was done by first performing a two-way ANOVA (BMDP program P2V) to determine whether drug and/or priming dose was a significant factor. When significant main effects were found, subsequent comparisons of drugs and priming doses were made by one-way ANOVA and by Fisher's protected least significant difference (LSD) (BMDP program P1V). A similar statistical procedure was followed for analysis of the time needed for T1% to reach 20%; i.e. two-way ANOVA was used as an initial screen to determine whether significant main effects existed, then one-way ANOVA and LSD were used for specific comparisons between drugs and between priming doses. In Phase II, analysis of the effects of different intubating doses on the overall time course of neuromuscular depression was done using repeated-measures ANOVA (BMDP program P2V) with intubating dose as the main factor and T1% measurements from 0 to 180 sec as the repeated measure. Statistical examinations of the effects of different intubating doses on degree of neuromuscular depression at 60, 80, and 100 sec, and of the effects on time for T1% ≤ 20%, were done using one-way ANOVA (BMDP program P1V). Categorical patient response data were analyzed using chi squared analysis (BMDP program P4F). In all statistical tests, a P value < 0.05 was considered significant. All values in tables are given as mean ± SD.

Results

Demographics between groups were similar. There was a broad distribution of age and weight within each group insuring the study covered the spectrum of patients usually seen in clinical practice.

The priming doses administered in both phase I and II resulted in some depression of neuromuscular transmission (Table 2). T1% was never less than 90% in all groups except for the group receiving 0.12 mg/kg atracurium (T1% = 75%). This priming dose of

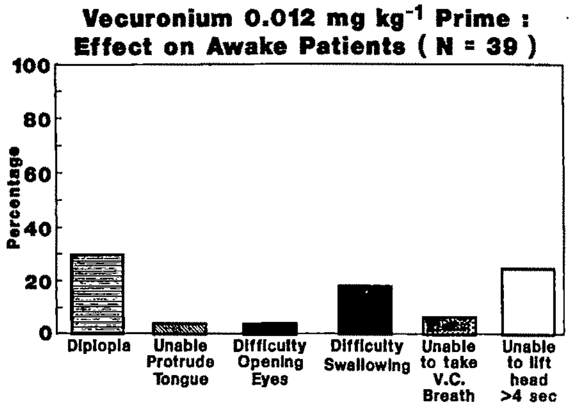

Figure 1. Effects of a priming dose of 0.012 mg/kg of vecuronium in the awake patient 3.5–4 min following its administration. V.C. = vital capacity.

atracurium also produced the largest reduction of T1% in any single patient (T1% = 50%). In the 50 patients evaluated following a priming dose of 0.012 mg/kg of vecuronium (10 from Phase I and 40 Phase II) the T1% showed a small decrease to 96% (range 71–100%). In phase II where the effects of the priming dose of 0.012 mg/kg vecuronium were evaluated in the awake patient, the most common adverse effect of this dose was diplopia (30%). A relatively large proportion of patients showed evidence of clinically significant neuromuscular weakness as evidenced by 25% of patients being unable to maintain head lift for 4 seconds and 20% of patients having difficulty swallowing (Fig. 1).

The time for the priming dose to produce a maximal measurable effect on T1% was similar between all three nondepolarizing muscle relaxants and for all four priming doses (Table 3). The average time among all groups for the maximal reduction in T1% produced by the priming dose was 4.7 ± 1.0 minutes. In all patients the maximal reduction in T1% produced by the priming dose was present prior to 7 minutes.

A significant effect of the priming dose compared to no prime was seen on the time course of neuromuscular blockade from when the intubating dose was given till 180 sec thereafter (Fig. 5, 2–4). There was also a significant difference in T1% at 60, 80, and 100 seconds between groups receiving a 15% priming dose (vecuronium 0.012 mg/kg, atracurium 0.09 mg/kg or pancuronium 0.015 mg/kg) and the groups receiving no prime (Table 4). Onset (T1% ≤ 20%) occurred significantly earlier in patients given a priming dose than in those who did not (Table 5). There was no statistically significant drug effect at each priming dose. There was also no significant drug prime interaction, i.e., at equivalent priming doses there was no differences between the drugs evaluated. When comparing the 15% priming doses of vecuronium, pancuronium and atracurium there was no significant difference between the three groups with respect to the time course of neuromuscular blockade, T1% at 60, 80 or 100 sec or the time for T1% ≤ 20%.

The T1% was significantly smaller at 60 and 80 seconds in the succinylcholine group than in patients receiving a priming dose equal to 15% of the total dose of atracurium (0.09 mg/kg), vecuronium (0.012 mg/kg) or pancuronium (0.015 mg/kg). At 100 sec there was still a significant difference in T1% between succinylcholine and pancuronium and vecuronium but not between succinylcholine and atracurium (Fig. 5). Onset of T1% ≤ 20% was significantly more rapid after succinylcholine than after priming with vecuronium (0.012 mg/kg) and pancuronium (0.015 mg/kg). Onset (T1% ≤ 20%) in patients given the 15% atracurium priming dose (0.09 mg/kg) could not be statistically differentiated from onset after succinylcholine, but the time for T1% ≤ 20% after succinylcholine was 66 ± 14 sec compared with 92 ± 32 sec following the 0.09 mg/kg atracurium priming dose (Table 5).

In phase II, where the priming dose of vecuronium was maintained at 0.012 mg/kg and the intubating dose increased from 0.068 mg/kg (in Phase I) to 0.08, 0.1, 0.12 and 0.15 mg/kg, neither the time course of neuromuscular blockade (T1% 0–180 sec—Figure 6) nor T1% at 60, 80 or 100 sec, nor the time taken to reach T1% ≤ 20% were significantly different between the groups.

Subjective evaluation of intubating conditions at 60 sec (Fig. 7) showed the overall assessment to be excellent in 90% of patients given succinylcholine. The overall intubating conditions following 0.012 mg/kg vecuronium (15% prime in Phase I) were excellent in 40%, satisfactory in 50% and fair in 10%. For 0.09 mg/kg atracurium (15% prime) intubation was considered excellent in 20%, satisfactory in 70% and fair in 10%. Pancuronium 0.015 mg/kg (15% prime) showed similar intubating conditions, being excellent in 30% and satisfactory in 70%. There was statistically no difference among the four groups.

The lack of shortening in onset time of neuromuscular blockade as evaluated by the evoked EMG in phase II, was also evident in the assessment of intubating conditions which showed similar intubating scores between the groups even though the intubating dose was increased (Fig. 8).

Discussion

In an effort to determine both the priming dose and

Table 3. Time (Minutes) to Maximal Effect of Priming Dose on T1% (Mean ± SD)

	Priming Dose as a Percent of Total Dose			
Drug (Total Dose)	5%	10%	15%	20%
Atracurium (0.6 mg/kg)	4.9 (± 1.0) N = 7	4.4 (± 0.4) N = 5	5.0 (± 1.0) N = 8	5.7 (± 1.1) N = 9
Vecuronium (0.08 mg/kg)	4.0 (± 0.6) N = 5	4.8 (± 1.0) N = 5	4.6 (± 0.9) N = 9	4.7 (± 1.2) N = 7
Pancuronium (0.1 mg/kg)	4.4 (± 0.9) N = 6	4.2 (± 0.7) N = 5	4.3 (± 0.9) N = 8	4.9 (± 0.8) N = 7

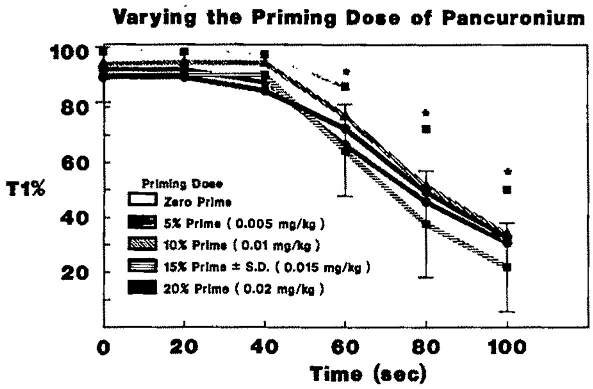

Figure 2. Time course of neuromuscular blockade measured by the decrease in T1% following no priming dose and priming doses of 5, 10, 15, and 20% of a total dose of 0.6 mg/kg of atracurium. Time zero also represents the maximum decrease in T1% following the administration of the priming dose. $^*P < 0.05$ in the difference in T1% between no priming dose and 5, 10, 15, or 20% priming doses at 60, 80 and 100 seconds.

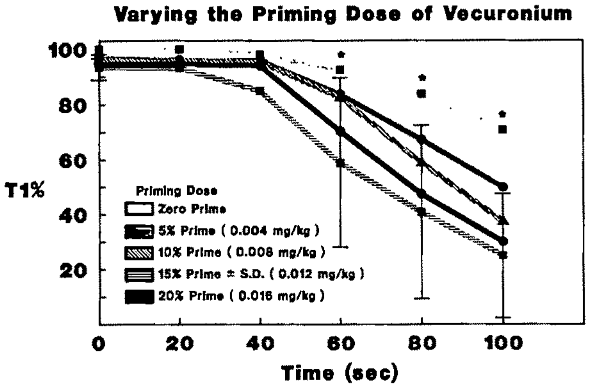

Figure 3. Time course of neuromuscular blockade measured by the decrease in T1% following no priming dose and priming doses of 5, 10, 15 and 20% of 0.08 mg/kg of vecuronium. Time zero also represents the maximum decrease in T1% following the administration of the priming dose. $^*P < 0.05$ in the difference in T1% between no priming dose and 5, 10, 15 or 20% priming doses at 60, 80 and 100 seconds.

intubating doses of atracurium, pancuronium and vecuronium producing the most rapid onset of neuromuscular blockade, we studied the effects of several different priming doses of atracurium, pancuronium and vecuronium, as well as different intubating doses for vecuronium. The "optimal" priming dose and intubating dose were then compared with succinylcholine as the standard for a rapid sequence induction. The study also attempted to establish if

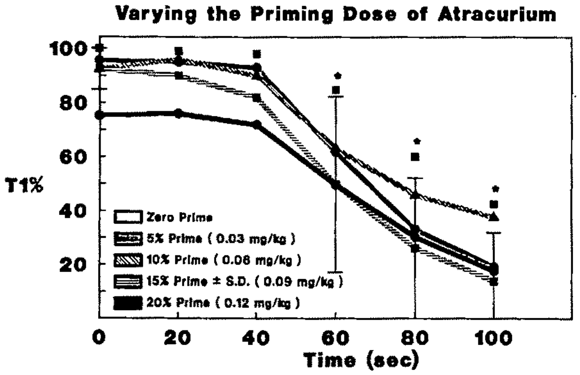

Figure 4. Time course of neuromuscular blockade measured by the decrease in T1% following no priming dose and priming doses of 5, 10, 15 and 20% of 0.1 mg/kg of pancuronium. Time zero also represents the maximum decrease in T1% following the administration of the priming dose. $^*P < 0.05$ in the difference in T1% between no priming dose and 5, 10, 15 or 20% priming doses at 60, 80 and 100 seconds.

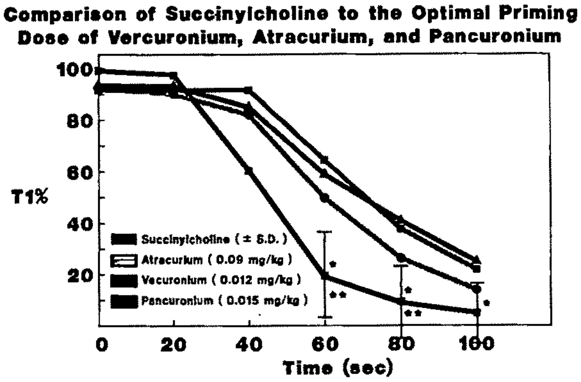

Figure 5. Comparison of the time course of neuromuscular relaxation between succinylcholine, and the optimal priming doses of atracurium (0.09 mg/kg) vecuronium (0.012 mg/kg) and pancuronium (0.015 mg/kg). $^*P < 0.05$ in the difference in T1% between succinylcholine pancuronium and vecuronium at 60, 80 and 100 seconds. $^{**}P < 0.05$ in the difference in T1% between succinylcholine and atracurium at 60 and 80 seconds.

Table 4. T1% at 60, 80 and 100 Seconds Following the Intubating Dose (Mean ± S.D.)

Drug/Priming Dose		60 Seconds	80 Seconds	100 Seconds
Atracurium	No Prime	84.8 (± 15)	60.1 (± 24)	42.7 (± 31)
	0.09 mg/kg	49.8 (± 33)*	26.2 (± 26)*	14.0 (± 18)*
Vecuronium	No Prime	92.6 (± 6)	83.8 (± 17)	70.8 (± 26)
	0.012 mg/kg	58.9 (± 31)*	40.8 (± 32)*	25.0 (± 23)*
Pancuronium	No Prime	87.6 (± 9)	72.2 (± 14)	50.1 (± 16)
	0.015 mg/kg	64.5 (± 17)*	37.6 (± 19)*	21.9 (± 16)*
Succinylcholine		17.1 (± 13)**	3.6 (± 4)**	1.6 (± 3)***

*Denotes $p < 0.05$ compared to no prime with same drug at same time interval.
**Denotes $p < 0.05$ compared to atracurium, vecuronium and pancuronium with a priming dose, at the same time interval.
***Denotes $p < 0.05$ compared to vecuronium and pancuronium with a priming dose, at the same time interval.

Table 5. Time (Seconds) for T1% To Reach 20% (Mean ± S.D.)

	Priming Dose as a Percent of Total Dose				
Drug (Total Dose)	0%	5%	10%	15%	20%
Atracurium (0.6 mg/kg)	146 (± 53)	106 (± 37)*	126 (± 53)	92 (± 32)*	102 (± 36)*
Vecuronium (0.8 mg/kg)	182 (± 46)	146 (± 33)*	130 (± 29)*	112 (± 36)*	110 (± 24)*
Pancuronium (0.1 mg/kg)	166 (± 28)	124 (± 42)*	132 (± 30)*	114 (± 23)*	130 (± 48)*
Succinylcholine (1.5 mg/kg)	66 (± 14)**				

*Denotes $p < 0.05$ compared to no prime dose of same drug.
**Denotes $p < 0.05$ compared to all groups except 15% atracurium priming dose.

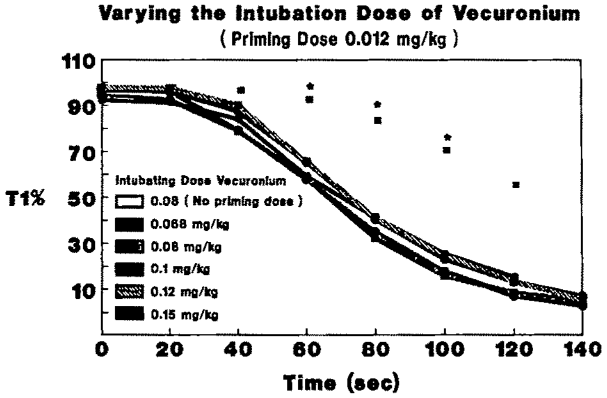

Figure 6. Time course of neuromuscular blockade measured by the decrease in T1% following either a 0.08 mg/kg vecuronium intubating dose with no priming dose or a 0.012 mg/kg priming dose and increasing intubating doses of 0.068, 0.08, 0.1, 0.12 mg, 0.15 mg/kg vecuronium. *$P < 0.05$ in the difference in T1% with 0.08 mg/kg with no priming dose and all other groups with a priming dose at 60, 80, 100 seconds.

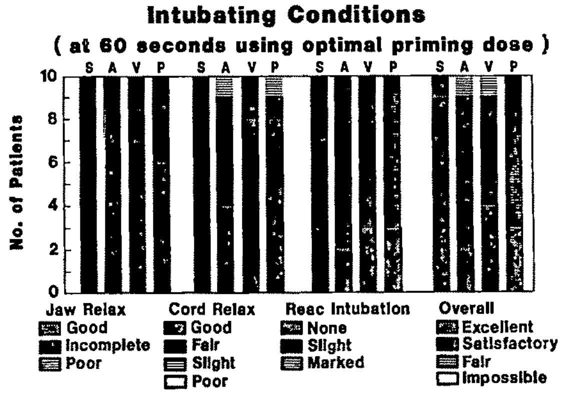

Figure 7. Assessment of intubating conditions 60 sec after administration of the intubating dose when priming doses of 0.012 mg/kg vecuronium, 0.09 mg/kg atracurium or 0.015 mg/kg pancuronium are given. Intubating conditions 60 sec following succinylcholine are also shown.

one of the three nondepolarizing relaxants showed a greater potential for enhancement in onset of neuromuscular blockade when the priming principle was used. Our results showed that priming even with small doses (0.03 mg/kg atracurium, 0.004 mg/kg vecuronium or 0.005 mg/kg pancuronium) enhanced onset of neuromuscular blockade as assessed by the time course of neuromuscular depression from 0–180 seconds, T1% at 60, 80 and 100 seconds and the time to reach T1% ≤ 20%. As the priming doses were increased to 0.09 mg/kg atracurium, 0.012 mg/kg vecuronium and 0.015 mg/kg pancuronium, there was a trend for onset to shorten. These priming doses had minimal effects on T1% prior to the intubating dose. A priming dose of 0.012 mg/kg vecuronium, however, produced clinical signs of muscle weakness in awake patients. Increasing the intubating dose of vecuronium from 0.068 to 0.15 mg/kg did not improve any of the parameters used to assess onset. Our results did not indicate that the use of a priming dose produced a greater effect on onset for any one of

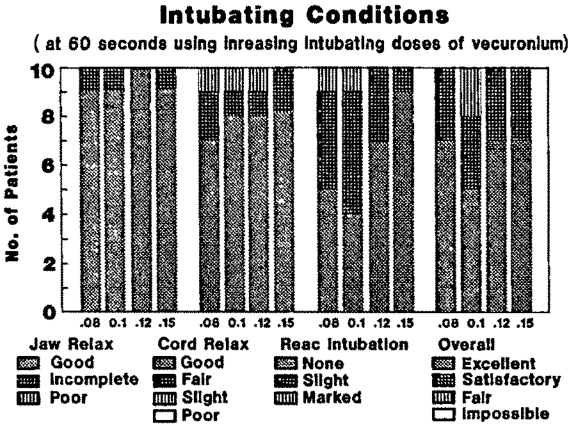

Figure 8. Assessment of intubating conditions 60 sec after an intubating dose of 0.08 mg/kg, 0.1 mg/kg, 0.12 mg/kg, or 0.15 mg/kg vecuronium when a priming dose of 0.012 mg/kg vecuronium is used.

the three nondepolarizing muscle relaxants evaluated (i.e., for the three nondepolarizing muscle relaxants priming reduced onset by approximately the same amount). Succinylcholine provided a greater depression of T1% at 60 seconds than any of the three nondepolarizing muscle relaxants even when their "optimal" priming doses were used.

There are three components to the priming principle: the priming dose, the priming interval (i.e., the time between priming and intubating doses), and the intubating dose. The effectiveness of priming on reducing the time of onset of neuromuscular depression has been questioned by some authors (7,8). The probable reason for the lack of efficacy using priming, as noted by these authors, is the importance of each component. Previous studies have evaluated systematically the "optimal" priming dose of vecuronium (9,10), but we are unaware of any study systematically establishing optimal priming doses for pancuronium or atracurium. Our results showing the "optimal" priming dose of vecuronium to be 0.012 mg/kg is midway between those reported by Taboada et al. (9) (0.01 mg/kg) and those of Kunjappan et al. (0.015 mg/kg) (10). The "optimal" priming dose that we established for pancuronium 0.015 mg/kg is the same as that reported by Mehta et al. (5), but greater than that reported by other authors (11,12) (0.007 mg/kg). The "optimal" priming dose for atracurium in this study was 0.09 mg/kg. This dose is similar to the dose used by Gergis et al. (0.08 mg/kg) in the first description of priming with atracurium (1). Subsequent studies with atracurium however have tended to use lower priming doses (8,13,14).

The priming interval was not systematically evaluated in this study, though the time for the priming dose to produce its maximal effect on T1% was measured. It is interesting to note that, in studies in which the priming interval was systematically varied (9,14), the optimal priming interval was 3–5 minutes for atracurium and 4 minutes for vecuronium. This was similar to the time taken for the maximal depression of T1% to occur following a priming dose in our study (i.e., 4.5 min). We also found the time to maximal reduction of T1% following a priming dose was similar for the three nondepolarizing muscle relaxants studied.

The "optimal" intubating dose of vecuronium has been evaluated by Taboada et al. (9) and Kunjappan et al. (10). Both of these studies found 0.1 mg/kg to be the "optimal" intubating dose. Neither study was able to show any improvement in onset by increasing the intubating dose to 0.15 mg/kg. Although we did not see any advantage in increasing the intubating dose above 0.068 mg/kg, our results confirmed these previous findings that with vecuronium there is no shortening of onset of neuromuscular blockade as the intubating dose is increased from 0.68 mg/kg to 0.15 mg/kg following a priming dose.

The major adverse effect of priming is the muscle weakness produced by the priming dose. Large priming doses have been associated with both severe muscle weakness and with aspiration (15). It is therefore important to determine the effects of the priming dose on the awake patient. The priming dose producing the most rapid onset as established in this study, produced only a small depression of T1%, but clinical signs of muscle weakness in awake patients following a priming dose of 0.012 mg/kg of vecuronium were common. The small decrease noted in T1% resulting from the priming dose may be the result of the methods used to measure T1%. The EMG shows about 15% less depression of T1% than the mechanomyogram (16). Other investigators have also evaluated the effect of muscle weakness of a priming dose (9,17,18). They also found a significant incidence of clinical muscle weakness with priming doses greater than 0.01 mg/kg of vecuronium. Pancuronium 0.01 and 0.15 mg/kg can also produce signs of clinical muscle weakness (17). None of our awake patients became distressed as a result of the priming dose but all were forewarned of possible muscle weakness and were mildly sedated. Therefore, it appears from our results that the priming dose producing the most rapid onset of neuromuscular blockade ("optimal" priming dose) is associated with a significant incidence of unpleasant side effects. If a priming dose is to be used it is essential to inform the patient of possible muscle weakness and to be vigilant for marked muscle weakness in those patients sensitive to nondepolarizing muscle relaxants.

By evaluating 3 nondepolarizing muscle relaxants simultaneously we were able to establish that priming is equally effective with all 3 agents. Thus, priming doses of vecuronium 0.012 mg/kg, pancuronium 0.015 mg/kg and atracurium 0.09 mg/kg are equally appropriate to use to produce a more rapid onset of neuromuscular blockade.

The onset of neuromuscular blockade was most rapid with succinylcholine even when the "optimal" priming dose was used. Thus, even though a priming dose reduces onset of neuromuscular blockade with atracurium, vecuronium and pancuronium, it is not equal to that following succinylcholine.

Priming using the appropriate priming dose, priming interval and intubating dose for vecuronium, pancuronium and atracurium can be used for rapid sequence intubation. Priming, however, has limitations due to varying sensitivities of patients to nondepolarizing neuromuscular blockers resulting in a significant incidence of symptoms of muscle weakness.

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The Effects of Anesthetics and $PaCO_2$ on the Cerebrovascular, Metabolic, and Electroencephalographic Responses to Nitrous Oxide in the Rabbit

Reiji Kaieda, MD, Michael M. Todd, MD, and David S. Warner, MD

KAIEDA R, TODD MM, WARNER DS. The effects of anesthetics and $PaCO_2$ on the cerebrovascular, metabolic, and electroencephalographic responses to nitrous oxide in the rabbit. Anesth Analg 1989;68:135–43.

The effects of nitrous oxide (N_2O) on cerebral blood flow and metabolism, intracranial pressure (ICP), the electroencephalogram etc. has been well described, at least when N_2O is used alone. However, during neurosurgical procedures, N_2O is almost always given in combination with either volatile or intravenous agents, and generally after the institution of some degree of hypocarbia. Unfortunately, the modifying influence of such interventions are not well known, and, therefore, the cerebral effects of 70% N_2O were studied in rabbits anesthetized with either 1 MAC halothane or isoflurane, or with a fentanyl/pentobarbital combination, during both normocarbia ($PaCO_2 \approx 40$ mm Hg) and hypocarbia ($PaCO_2 \approx 20$ mm Hg). Cortical cerebral blood flow (CBFc) and sagittal sinus blood flow (CBFss—as an index of "global" forebrain flow) were measured using the hydrogen clearance method. Cerebral oxygen consumption ($CMRO_2$) was calculated, and intracranial pressure (ICP), central venous pressure, heart rate, mean arterial pressure, and the EEG were also recorded.

CBFc during normocarbic halothane, isoflurane, and fentanyl-pentobarbital anesthesia was 69 ± 23, 41 ± 16, 53 ± 26 $ml \cdot 100g^{-1} \cdot min^{-1}$ (mean ± SD) respectively, with a significant difference between halothane and isoflurane. The addition of 70% N_2O to all three anesthetics significantly increased CBFc by 32%, 34% and 36% respectively during normocarbia and by 47%, 65% and 27% during hypocarbia. A similar pattern was seen for CBFss. There were no significant differences in the response to N_2O based either on anesthetic or $PaCO_2$, except that the increase in CBFss produced by N_2O during normocarbic fentanyl-pentobarbital anesthesia (10%) was less than that noted during normocarbic halothane anesthesia (39%). $CMRO_2$ was not changed by addition of N_2O regardless of anesthetic or $PaCO_2$. N_2O increased ICP under all conditions; the increments were small (about 1 mm Hg). The greatest EEG changes in responses to N_2O were seen in halothane-anesthetized animals (a decrease in amplitude and increase in frequency). In contrast, no consistent EEG changes were seen with N_2O in the fentanyl/pentobarbital group, while the only effect observed in the presence of isoflurane was the disappearance of the typical burst-suppression pattern. We conclude that N_2O increases CBF and ICP with each of the three background anesthetics during both normocarbia and hypocarbia. The magnitude of this response to N_2O may be less during a fentanyl/barbiturate based anesthetic. These changes were not associated with alterations in $CMRO_2$, suggesting that N_2O may be a direct cerebral vasodilator in this species.

Key Words: ANESTHETICS, GASES: nitrous oxide. ANESTHETICS, VOLATILE: halothane, isoflurane. ANESTHETICS, INTRAVENOUS: fentanyl, pentobarbital. BRAIN: blood flow, electroencephalogram. ANESTHESIA, neurosurgical.

Nitrous oxide (N_2O) increases intracranial pressure (ICP) (1,2) and cerebral blood flow (CBF), both when give alone (3,4) and in combination with halothane (2,5–7) or isoflurane (8). Under some circumstances, these changes are associated with an increase in cerebral metabolic rate for oxygen ($CMRO_2$) (2,4,5,9). Nevertheless, N_2O is still commonly used for neurosurgical anesthesia, usually in combination with other anesthetics, since it is felt that these cerebrovascular effects are blocked by hypocarbia and/or by some intravenous anesthetics (e.g., barbiturates) (2,10). However, we recently noted that hypocarbia

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Address correspondence to Dr. Todd, Department of Anesthesia, GH6SE, University of Iowa Hospitals and Clinics, Iowa City, IA 52242.

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did not block the increase in CBF produced by N_2O in halothane anesthetized rabbits (11), while Drummond et al. demonstrated that the CBF changes seen with 70% N_2O were similar when the agent was added to either a halothane or isoflurane background, and that these changes were not altered by the administration of morphine (12).

Unfortunately, with the exception of the work of Drummond et al., there have been no attempts to examine *concurrently* the influence of anesthetics and $PaCO_2$ on both the cerebrovascular, metabolic and electroencephalographic responses to N_2O. Therefore, in an effort to provide a more coherent answer to these questions, we compared the changes in CBF, $CMRO_2$, ICP and the EEG produced by 70% N_2O given to rabbits anesthetized with either 1 MAC halothane (1.39%) (13) or isoflurane (2.05%) (13), or with a fentanyl (100 $\mu g/kg$ iv, then 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$)/ pentobarbital (15 mg/kg iv) combination, during both normo- and hypocarbia.

Methods

Twenty-four New Zealand white rabbits of either sex, weighing 3.5 ± 0.3 kg (mean ± S.D.) were studied. All experiments were approved by the University of Iowa School of Medicine Animal Use Committee.

All animals received one of three anesthetics: Group 1 rabbits ($n = 8$) received halothane, Group 2 ($n = 8$) received isoflurane, and Group 3 animals ($n = 8$) were given a fentanyl/pentobarbital combination.

Preparation

Anesthesia was induced with either halothane or isoflurane in a closed plastic box. A 22 g catheter was inserted into a marginal ear vein, and the trachea intubated with a 3.0 mm ID cuffed tube (Mallinckrodt). Pancuronium, 1 mg was then given intravenously and mechanical ventilation begun using a tidal volume of 15 ml/kg at a rate of 35 breaths per minute, with an inspired gas mixture of ≈1.5% halothane or 2% isoflurane in 70% nitrogen (N_2)/ balance oxygen (O_2). This ventilatory pattern normally resulted in hypocarbia ($PaCO_2 \approx 20$ mm Hg), and CO_2 was added to the inspired gas mixture to maintain normocarbia ($PaCO_2 \approx 40$ mm Hg) as initially assessed by expired gas analysis and later by arterial blood gas tensions. A thermistor was passed into the esophagus, and the animal's temperature was maintained at 38°C using a servocontrolled warming pad, while a maintenance infusion of lactated Ringer's solution was given at a rate of 4 $ml \cdot kg^{-1} \cdot h^{-1}$. Pancuronium was added to this fluid in amounts sufficient to insure the delivery of ≈1 mg of drug per hour.

The animal was then turned supine, 0.25% bupivacaine was infiltrated into the groin area, and PE-90 catheters were surgically inserted into the abdominal aorta and the right atrium via the femoral vessels, with the atrial catheter positioned by examination of the transduced pressure waveform (usually during pullback from the right ventricle). The catheters were secured, the animal was turned to the prone position and the head fixed into a stereotactic frame (David Kopf Instruments) with the interaural line ≈10 cm above the mid-chest. The scalp was infiltrated with 0.25% bupivacaine (total dose <12.5 mg), and a midline incision made. The scalp was reflected bilaterally. The bregma (the crossing of the sagittal and coronal sutures) was carefully marked, and three 2.0 mm diameter burr holes were drilled, two located 5 mm anterior to the bregma and 5 mm to the left and right of the midline (frontal) and one located 9 mm posterior and 8 mm to the right of the midline (right parietal). The confluence of cerebral venous sinuses was also exposed, as well as ≈1 cm of the sagittal sinus anterior to the confluence. A PE-50 catheter was then inserted into the confluence via the sagittal sinus, with its position adjusted to permit free aspiration of cerebral venous blood. An 18g Tuohy needle was stereotactically inserted into the lateral ventricle via the right parietal burr hole, and finally 250μm diameter platinum needle electrodes (Grass Instruments E2 subdermal electrodes™) were placed into the exposed venous confluence, and into left and right frontal grey matter via the frontal burr holes. These latter two electrodes were inserted a distance of 2 mm beyond the point of dural contact. All holes were then sealed with Permabond 910™ cyanoacrylate cement. Two additional needle electrodes were placed into the scalp at each end of the coronal suture to permit the recording of a single channel biparietal EEG, and a Ag-$AgCl_2$ EKG electrode was placed on a shaved area of skin on the animals back to serve as a reference electrode for CBF determinations.

After surgical preparation was complete, and correct performance of all equipment and catheters was confirmed, end-tidal concentrations of the volatile anesthetics were adjusted to values of 1 MAC (1.39% halothane, 2.05% isoflurane) (13). These concentrations were maintained for a minimum of 30 minutes before the first measurements were recorded (see below).

Animals in Group 3 underwent a surgical preparation identical to that in Groups 1 and 2. However, anesthesia in half of these animals was initially induced with halothane, while in the remainder were given isoflurane. Immediately after the arterial catheter was placed, administration of the volatile anesthetic was discontinued, and 15 mg/kg of pentobarbital was slowly given intravenously. Approximately 5 minutes after completion of pentobarbital injection, fentanyl 100 μg/kg was given as a loading dose, followed by a continuous infusion of fentanyl at a rate of 25 $\mu g \cdot kg^{-1} \cdot h^{-1}$, an infusion rate that was continued throughout the remainder of the experiment. Immediately after the placement of all electrodes and cannulas, each animal received an additional 7.5 mg/kg dose of pentobarbital. In 3 of the animals in this group, a third pentobarbital dose was given (7.5 mg/kg) upon completion of the first nitrogen-N_2O pair of measurements (see below). This was done because of hemodynamic and/or electroencephalographic signs of inadequate anesthesia (i.e., hypertension associated with a change to lower amplitude-higher frequency EEG activity in the absence of N_2O). This supplementary dose was given at least 20–30 minutes before any subsequent measurements. End-tidal volatile agent concentration at the time of all CBF/CMR measurements was <0.05%. (It has not proven possible to anesthetize a rabbit with high doses of narcotics alone, at least without seizure activity. Therefore, to achieve an adequate anesthetic, some "sedative" supplementation is required. However, it should be noted that the doses of pentobarbital given to our rabbits are not anesthetic in themselves, and serve only as sedatives. Thus, the described fentanyl-pentobarbital combination is a primarily narcotic-based anesthetic. However, while the doses have been chosen to roughly approximate "1MAC" (based on preliminary tail-clamp studies), rigidly quantitative comparisons of anesthetic depth between this group and the volatile agent groups is difficult.)

Continuously displayed variables in all animals included esophageal temperature, FiO_2, expired CO_2 and volatile agent concentrations, mean arterial pressure (MAP), central venous pressure (CVP), ICP and EEG. All pressures are expressed as electrical means at end-expiration. Heart rate (HR) was calculated manually from the arterial pressure recording. The EEG was recorded both on paper (Grass polygraph) along with other variables, and on magnetic tape for latter computer processing, which was performed using a Tracor Northern "Nomad™" system. Arterial and cerebral venous blood samples (1 ml volumes) were intermittently sampled for measurement of blood gas tensions, total hemoglobin concentration, and percent oxyhemoglobin. These latter values, obtained using an IL 282 Cooximeter™, were used to calculate arterial and cerebral venous O_2 contents [content $O_2 = (1.34 \times \text{Hb} \times \%\text{saturation}) + 0.003 \times PaO_2$].

CBF was measured from each of the three platinum electrodes (cortex and venous sinus) using the hydrogen (H_2) clearance method (14). H_2 gas (3–5%) was added to the inspired gas mixture until a stable plateau current was achieved. H_2 was then abruptly discontinued, and CBF calculated by the $T_{1/2}$ method (15), after discarding the initial 30 sec of the washout curve. Cortical CBF (CBFc) was calculated as the average of the left and right cortical flow values, while flow measured in the confluence of venous sinuses is abbreviated as CBFss. $CMRO_2$ was calculated as the product of CBFss and arterial-venous oxygen content differences.

Experimental Protocol

All experiments consisted of two pairs of measurements. In each pair, initial measurements were made during ventilation with 70% N_2 in O_2, then again during the administration of 70% N_2O. The reverse order was not studied. One pair of measurements was obtained under normocarbic conditions ($PaCO_2 \approx 40$ mm Hg), while the second pair of measurements was obtained during hypocarbia ($PaCO_2 \approx 20$ mm Hg). In half of the animals, the first pair of recorded data (N_2-N_2O) was obtained during hypocarbia (followed later by normocarbia), while in the remainder, the first measurements were made during normocarbia (with later hypocarbia). To simplify description, only the detailed protocol for the "normocarbic-hypocarbic" sequence will be described.

Thirty minutes after completion of the surgical procedure, an arterial blood sample was drawn to verify normocarbia. The H_2 was then added to the inspired gas mixture. Seven to 10 minutes later, hemodynamic variables were recorded (HR, MAP, RAP, ICP) along with the EEG. Arterial and cerebral venous blood samples were obtained, and H_2 was discontinued. The actual recording of the hydrogen clearance curve required about 10 additional min. When completed, N_2 was replaced with 70% N_2O. About 7 minutes later, H_2 gas was again introduced, and 7 to 10 minutes later (≈15 min after turning on N_2O), the above sequence of measurements was repeated. When clearance curves were completed, N_2O was again replaced with N_2. Five minutes later, CO_2 concentration in the inspired gas mixture was reduced, thus decreasing end-tidal CO_2 to ≈15–20 mm Hg over 10 min. This was held constant for another 15 minutes after blood sampling verified the

Table 1. Physiologic Variables

Anesthetic	CO_2/N_2O		HR (beats/min)	MAP (mm Hg)	PaO_2 (mm Hg)	$PaCO_2$ (mm Hg)	pH (units)
Halothane (n = 8)	Normo	N_2	267 ± 27	75 ± 5	171 ± 13	40 ± 2	7.37 ± 0.04
		N_2O	$284 \pm 22^{*}$	76 ± 5	169 ± 11	41 ± 2	7.37 ± 0.04
	Hypo	N_2	283 ± 25	74 ± 4	170 ± 14	21 ± 1	7.56 ± 0.04
		N_2O	$298 \pm 32^{*}$	$78 \pm 7^{*}$	171 ± 17	21 ± 2	7.53 ± 0.04
Isoflurane (n = 8)	Normo	N_2	270 ± 26	72 ± 6	175 ± 8	41 ± 2	7.38 ± 0.05
		N_2O	284 ± 26	73 ± 4	170 ± 8	41 ± 3	7.37 ± 0.06
	Hypo	N_2	279 ± 8	71 ± 5	169 ± 8	22 ± 2	7.57 ± 0.06
		N_2O	$299 \pm 30^{*}$	73 ± 3	159 ± 12	21 ± 2	7.55 ± 0.06
Fentanyl/Pentobarbital (n = 8)	Normo	N_2	$216 \pm 26^{\bullet}$	$86 \pm 6^{\bullet}$	166 ± 7	40 ± 2	7.37 ± 0.05
		N_2O	$253 \pm 30^{*\bullet}$	$96 \pm 7^{*\bullet}$	162 ± 7	42 ± 2	7.37 ± 0.04
	Hypo	N_2	$278 \pm 29\#$	$88 \pm 8^{\bullet}$	163 ± 8	21 ± 2	7.55 ± 0.05
		N_2O	$298 \pm 36\#$	$92 \pm 12^{\bullet}$	162 ± 7	22 ± 1	7.52 ± 0.04

All values are expressed as mean ± SD. Normo = normocarbia, Hypo = hypocarbia. HR = heart rate, MAP = mean arterial pressure.
Statistics: *: $p < 0.05$, N_2O vs N_2 (nitrous effect)
$^{\bullet}$: $p < 0.05$, Fentanyl/Pentobarbital vs. Halothane and Isoflurane
#: $p < 0.05$, Hypo vs Normocarbia

desired degree of hypocarbia, and the above noted paired sequence of recordings during N_2 and N_2O administration were repeated.

Since arterial blood pressure may be an important determination of CBF, particularly during the administration of volatile anesthetics, an effort was made to insure that a minimum MAP of 65–70 mm Hg was maintained at all times and that the MAP during both components of the N_2-N_2O pair was similar. In the two volatile agent groups, this was accomplished when necessary, by the intravenous infusion of a dilute solution of angiotensin II (human form, synthetic, Sigma Chemical). However, in Group 3 (fentanyl/pentobarbital), hypertension was the more common problem. To minimized the BP differences between groups, BP was kept <100 mm Hg in these animals either by the removal of up to 20 ml of arterial blood and/or the administration of trimethaphan intravenously.

EEG Analysis

Signals for EEG were recorded on a Grass polygraph with low and high frequency cutoffs of 0.3 Hz and 30 Hz respectively, with a supplemental 60Hz notch filter. Gain was set at 100 μV/cm pen deflection. These signals were also recorded on FM tape (Vetters Model C4), and were later subjected to a Fourier analysis as performed by a Tracor NOMAD™ system, using 4-second epochs. Quantitated variables included total electrical power, peak power frequency, spectral edge (95%), median power frequency, and percent distribution of power into delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (>13 Hz) frequency bands (power spectrum).

Statistical Analysis

The effect of anesthetics, $PaCO_2$, and N_2O were evaluated by a three factor (anesthetic, $PaCO_2$, N_2 vs. N_2O) analysis of variance (ANOVA) with N_2 vs. N_2O as a repeated measure. Pair-wise Newman-Keuls tests were used as indicated (to compare anesthetics), while the response to N_2O within an anesthetic group at a given $PaCO_2$ was subsequently examined when indicated using a paired t-test. All data are reported as mean ± SD, and statistical significance was assumed for $p < 0.05$. Statistical calculations (except for Newman-Keuls tests) were performed on a Macintosh computer, using a commercial statistical package (StatView 512+™, BrainPower Inc.).

Results

There was no intergroup differences in either weight or sex ratio. HR, MAP, PaO_2, $PaCO_2$ and pH in the three groups, with and without N_2O, are summarized in Table 1. The three different anesthetics had clearly different hemodynamic effects, with MAP being higher in the fentanyl/pentobarbital group. Furthermore, in two of eight fentanyl/pentobarbital animals, trimethaphan was given, and in one animal, 20 ml of blood were withdrawn to control MAP. In contrast, essentially all animals in the halothane and isoflurane groups received angiotensin to maintain MAP (with

Table 2. CBF, $CMRO_2$ and ICP

Anesthetic	CO_2/N_2O		CBF_c $ml \cdot 100g^{-1} \cdot min^{-1}$	CBFss $ml \cdot 100g^{-1} \cdot min^{-1}$	$CMRO_2$ $ml \cdot 100g^{-1} \cdot min^{-1}$	ICP mm Hg
Halothane (n = 8)	Normo	N_2	69 ± 23	71 ± 30	3.7 ± 1.4	4 ± 2
		N_2O	$89 \pm 29^{*}$	99 ± 40	3.8 ± 1.1	$6 \pm 2^{*}$
	Hypo	N_2	56 ± 21	$57 \pm 12\#$	4.0 ± 1.2	5 ± 2
		N_2O	$76 \pm 18^{*}$	$68 \pm 17^{*}\#$	4.0 ± 0.9	$6 \pm 2^{*}$
Isoflurane (n = 8)	Normo	N_2	$41 \pm 16^{\bullet h}$	65 ± 23	2.7 ± 1.1	7 ± 2
		N_2O	$53 \pm 19^{*\bullet h}$	$82 \pm 34^{*}$	2.6 ± 0.8	$8 \pm 3^{*}$
	Hypo	N_2	$29 \pm 13\#^{\bullet h}$	$48 \pm 22\#$	3.2 ± 0.8	6 ± 2
		N_2O	$49 \pm 35^{*}$	$65 \pm 29^{*}$	3.7 ± 1.6	$7 \pm 2^{*}$
Fentanyl/Pentobarbital (n = 8)	Normo	N_2	53 ± 26	58 ± 27	$4.9 \pm 1.1^{\bullet i}$	6 ± 4
		N_2O	$72 \pm 35^{*}$	$64 \pm 28^{*}$	$5.2 \pm 1.3^{\bullet i,h}$	$7 \pm 2^{*}$
	Hypo	N_2	$41 \pm 14\#$	43 ± 15	$4.7 \pm 1.6^{\bullet h}$	6 ± 2
		N_2O	$51 \pm 20\#^{*}$	$48 \pm 24\#^{*}$	4.8 ± 1.6	$7 \pm 3^{*}$

All values are expressed as mean ± SD. Normo = normocarbia, Hypo = hypocarbia. CBFc = cortical cerebral blood flow, CBFss = sagittal sinus blood flow.
Statistics: *: $p < 0.05$, N_2O vs N_2 (nitrous effect)
$^{\bullet}$: $p < 0.05$, different from other anesthetic group, *h* = halothane, *i* = isoflurane
#: $p < 0.05$, Hypo vs Normocarbia

no halothane vs. isoflurane intergroup differences in either the number of animals requiring the drug or the dose of angotensin given). There were no differences in PaO_2, $PaCO_2$ or pH between three anesthetic groups, and N_2O administration resulted in no changes. Hemoglobin concentrations ranged from 11.2 to 11.7 g/dl, while CVP ranged from 1 to 4 mm Hg, again with no intergroup, $PaCO_2$, or N_2O related differences.

HR increased significantly with administration of N_2O in all 3 groups, under both normo- and hypocarbic conditions. However, the only significant increase in MAP with N_2O occurred during normocarbic fentanyl/pentobarbital anesthesia.

As expected, CBF (both CBFc and CBFss) was significantly lower during hypocarbia than during normocarbia within each of the 3 anesthetic groups (Table 2). In addition, CBFc values were significantly lower in the presence of isoflurane than during either halothane or fentanyl/pentobarbital anesthesia at a given $PaCO_2$. However, no intergroup differences were noted in CBFss at similar $PaCO_2$'s. $CMRO_2$ was significantly higher in normocarbic fentanyl/pentobarbital animals than in either halothane or isoflurane groups, although this difference was lost during hypocarbia ($p = 0.082$). The difference in $CMRO_2$ between halothane and isoflurane animals did not achieve statistical significance at either $PaCO_2$ (e.g., during normocarbia, $CMRO_2$ for halothane = 3.7 ± 1.1 $ml \cdot 100g^{-1} \cdot min^{-1}$ vs. 2.7 ± 1.1 $ml \cdot 100g^{-1} \cdot min^{-1}$ for isoflurane, $0.05 < p < 0.10$).

There were no significant changes in $CMRO_2$ associated with the administration of N_2O during either normocarbia or hypocarbia, regardless of anesthetic. 70% N_2O increased both CBFc and CBFss significantly in all three groups, during both normocarbia and hypocarbia, with the magnitude of such increases ranging from 11 to 65%. Intergroup comparisons of the magnitudes of these N_2O-mediated increases revealed only a single statistically significant difference, i.e., the increase in CBFss produced by N_2O during normocarbic fentanyl/pentobarbital anesthesia (10% increase) was less than that seen with normocarbic halothane (39%) although it was not different from that seen with isoflurane (26%). A similar pattern was noted during hypocarbia (i.e., 11% increase in fentanyl/pentobarbital animals, vs. 35% and 20% increases in the isoflurane and halothane groups respectively), but the differences did not achieve statistical significance.

ICP increased with N_2O during both normocarbia and hypocarbia, although only by 1 to 2 mm Hg. There were no differences between the anesthetics.

Baseline EEG patterns produced by the three anesthetics were clearly different, although we were unable to define any effects of $PaCO_2$ during N_2 ventilation. Representative examples recorded during hypocarbia are shown in Figure 1. During the administration of isoflurane administration, a pattern of burst suppression was almost uniformly seen, which made quantitative processing difficult. By contrast, halothane and fentanyl/pentobarbital animals all had continuous EEG activity. In the halothane group, the EEG was characterized by relatively rhythmic (4–6 Hz), high amplitude (100 μV), with an upper frequency limit (Spectral Edge) of ≈18 Hz. The patterns seen with fentanyl/pentobarbital were less rhythmic, with fewer slow waves, a much lower total

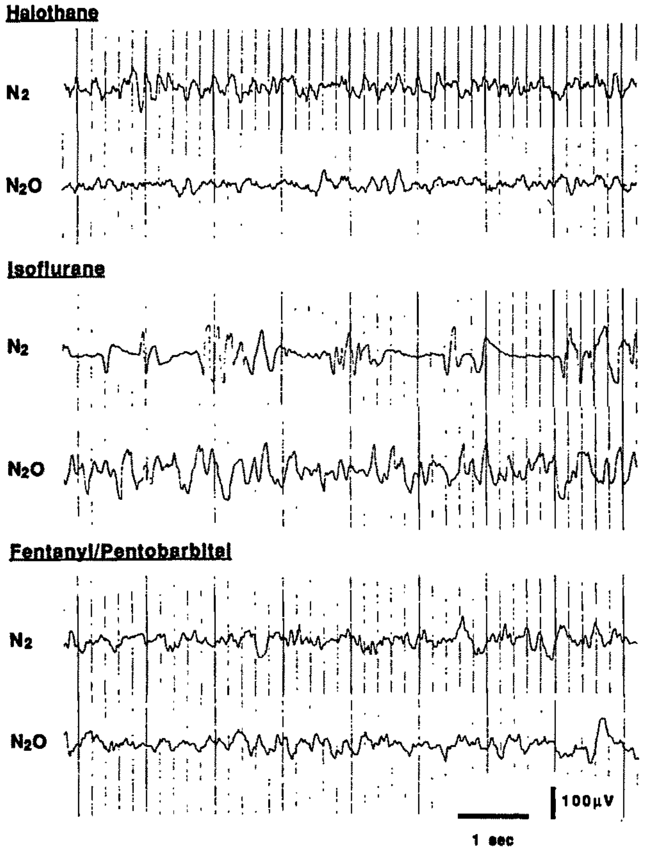

Figure 1. Biparietal EEG recordings illustrate the response to N_2O during the three background anesthetic states (all recordings obtained during hypocarbic conditions). With 1 MAC halothane (upper two traces), the addition of 70% N_2O reduced amplitude and increased frequency. With 1 MAC isoflurane (middle two traces), the typical burst suppression patterns were reversed by N_2O. With the fentanyl/pentobarbital combination (lower two traces), there are no typical changes associated with the addition of N_2O.

power than seen with halothane (e.g. mean values of ≈9000 μV^2 vs 26000 μV^2 respectively), and a slightly lower spectral edge (15–16 Hz).

The introduction of N_2O had detectable effects only in the halothane and isoflurane groups. With a halothane background, N_2O produced a major decrease in amplitude (e.g. expressed as a reduction in total power from 26000 to ≈6000 μV^2), an almost total loss of low frequency activity (although some occassional theta waves remained), and an increase in spectral edge (from 18 to 21 Hz). In isoflurane anesthetized animals, the most striking response to N_2O was a loss of the burst suppression background pattern, which was converted to relatively high amplitude, mixed frequency activity.

We were unable to define any consistent response to N_2O in fentanyl/pentobarbital animals, although quantitative processing revealed some statistically significant changes in frequency parameters (e.g. a 0.8-Hz increase in peak power frequency, a 0.8-Hz reduction in spectral edge etc). None of these changes were consistently apparent by visual inspection of the raw EEG traces, or by examination of the color density spectral array (CDSA) display of the processing unit.

Discussion

Many investigators have noted the ability of N_2O to increase CBF (2–8), ICP (1,2) and sometimes $CMRO_2$ (2,4,5,9), at least under some situations. However, N_2O is almost always used in combination with other agents, and there are few studies examining the influence of these other drugs, or examining the role of $PaCO_2$ in modifying the cerebrovascular responses N_2O. Furthermore, most of the available studies have examined only small portions of the question, e.g., looking at only one anesthetic, examining the role of $PaCO_2$ alone, failing to examine $CMRO_2$ responses, etc. The current experiments were therefore undertaken in an effort to concurrently examine several of these interrelated questions.

Before discussing our results, several methodological aspects of these experiments deserve comment. Our studies were performed during stable background anesthetics, with measurements made before and after the addition of 70% N_2O. While published data concerning the MAC-contribution of N_2O in the rabbit are sparse, we believe this to represent ≈0.5 MAC (see the Discussion section of Reference 11). As a result, examination of the CBF response to N_2O in the halothane and isoflurane groups represented a comparison of a 1 MAC anesthetic (volatile agent + N2) with a 1.5 MAC anesthetic (volatile agent + 0.5 MAC N_2O). It is possible that other conditions (e.g., 1 MAC volatile agent compared with 0.5 MAC volatile agent + 0.5 MAC N_2O) might yield different conclusions. However, the work of Manohar et al. suggests that this is not the case (7,8). Furthermore, it is perhaps not appropriate to compare either of the two volatile agent groups with the fentanyl/pentobarbital animals (to which a "MAC fraction" cannot be assigned). As noted in the Methods section the intravenous anesthetic technique we used was designed as a narcotic-based anesthetic. It is not possible to perform a narcotic-O_2 anesthetic in the rabbit without the production of seizures, and therefore, we chose a dose of fentanyl sufficient to produce marked respiratory depression and analgesia (minimal response to tail clamp = in spite of an apparently "awake" rabbit), and supplemented this with sedative doses of pentobarbital (doses that alone were not anesthetic). The specific goal was to achieve a "relevant" anesthetic state that was associated with CBF/CMR values different from that seen with the volatile agents. We believe that this goal was achieved, but also realize that quantitative comparisons of cerebrovascular differences between the two groups given volatile anesthetics and animals given fentanyl/pentobarbital must be tempered by recognizing these differences. As a specific example, the hemodynamic differences between the three anesthetics were readily apparent, with lower blood pressures in the halothane and isoflurane groups. Since the influence of BP on CBF is well known (particularly during the administration of volatile anesthetics), we chose to "fix" BP within a predetermined window. However, this required the administration of angiotensin in animals given the volatile agents, vs trimethaphan/phlebotomy in the fentanyl/pentobarbital group. Neither of these two vasoactive drugs are thought to have significant direct effects on the cerebral vasculature when given in modest intravenous doses, although the changes in BP will influence measured CBF (as intended) (16,17). However, such differences in hemodynamics and/or pharmacologic intervention should make us cautious about overinterpreting intergroup differences.

Our results are also dependent on the measurement methods used. We quantitated CBF by the hydrogen clearance method (14), a technique that measures flow in a relatively small volume of tissue surrounding the tip of the electrodes. As a result, implanted cortical electrodes provide flow values (designated CBFc) that may not be representative of whole brain CBF (although they probably yield flow data that is representative of the entire cortex). In particular, the use of such cortical CBF data may lead to erroneous calculations of $CMRO_2$, since the measured venous blood sample may not be representative of the same tissue compartment as that "seen" by the CBF electrode. However, Scremin et al. (18) inserted an electrode into the sagittal sinus of rabbits, and noted a good correlation to volumetric flow measurements (blood collection). We therefore chose to place an electrode into the confluence of sinuses to measure a "forebrain" CBF (designated CBFss), and used this value to calculate $CMRO_2$, thereby eliminating the possibility of any "compartment" errors (since venous blood samples were also obtained from the confluence).

Given these caveats, our results indicate that N_2O significantly increases CBF when added to all three of the selected anesthetics, during both normocarbic and hypocarbic conditions. These observations are consistent with a number of earlier works demonstrating the effects of N_2O on CBF and ICP (2–8), but more importantly extend the recent studies of Drummond et al. (12) and Todd (11). Drummond et al. (12) observed similar N_2O mediated CBF increases during both normocarbic halothane and isoflurane anesthesia, while Todd (11) found that such increases in CBF were not blocked by hypocarbia during halothane anesthesia. Furthermore, the current work demonstrates that the magnitude of the CBF response to N_2O was not appreciably different between the two volatile agents, or between different $PaCO_2$ circumstances. The only anesthetic-mediated difference in N_2O response (a reduction in the magnitude of the CBF increase) was noted in the normocarbic fentanyl/pentobarbital group (with a suggestion of a similar effect during hypocarbia). This finding suggests that some anesthetics may modify the cerebral vascular responses to N_2O (10), although Drummond et al. (12) failed to observe any modifying effects of morphine on the response to N_2O during normocarbia. However, without a formal dose-response study, or a comparison of morphine vs fentanyl, we cannot firmly reconcile these differences. Of equal interest was the fact that these CBF changes were not associated with any N_2O-mediated alterations in $CMRO_2$. This was in spite of significant intergroup differences in $CMRO_2$ during N_2 ventilation which are consistent with published data (e.g., normocarbic halothane = 3.7 ± 1.1 $ml \cdot 100g^{-1} \cdot min^{-1}$, isoflurane = 2.7 ± 1.4 $ml \cdot 100g^{-1} \cdot min^{-1}$, fentanyl/pentobarbital = 4.9 ± 1.1 $ml \cdot 100g^{-1} \cdot min^{-1}$) (19,20). However, Theye et al. (9) observed a N_2O-mediated increase in $CMRO_2$ in dogs given a spinal anesthetic and breathing 0.1% halothane, while a similar observation was made by Takeshita and associates (2,5). Nevertheless, both groups showed marked attenuation of the $CMRO_2$ effect of N_2O when animals were ventilated with higher concentrations of halothane, and Sakabe et al. (2) noted that thiamylal also prevented N_2O-mediated increases. It therefore appears that any cerebral metabolic "stimulative" effects of N_2O are blocked by sufficient levels of background anesthesia.

This lack of any $CMRO_2$ effect of N_2O suggests that the CBF effects of N_2O are not mediated by metabolic changes, and in turn implies that the drug may be acting as a direct cerebral vasodilator. Other explanations are clearly possible, but it does not appear that the effect is directly related to electroencephalographic activation, as was speculated in a previous study from this laboratory (11). As expected, the EEG patterns produced by the three anesthetics were different. However, the EEG response to N_2O was also different among the three anesthetics, with a change being most visible during halothane (an increase in frequency and a decrease in amplitude) and isoflurane (a loss of the burst suppression pattern), but not apparent at all in the fentanyl/pentobarbital group. Yamamura et al. (21) reported that N_2O increased fast oscillatory actvities in unmedicated human volunteers, while Drummond et al. (12) also observed the disappearance of burst-suppression when N_2O was added to isoflurane anesthetized rabbits. By contrast, Sakabe et al. (22) reported that N_2O induced slow wave activities when added to humans breathing 0.84% halothane. These latter observations suggests that there may be major species-related differences in the EEG effects of N_2O, and also indirectly supports speculation that the other cerebrovascular and metabolic changes may be influenced by the choice of experimental subject. Nevertheless, it also indicates that changes in the EEG may or may not be closely related to the cerebrovascular or metabolic events that occur with drug administration, depending on the background anesthetic.

One final observation made in the course of this work deserves comment, although it does not directly relate to N_2O. This concerns differences in CBF as measured in the cortex and in the confluence of venous sinuses (a measure of global CBF) during halothane and isoflurane anesthesia. During 1 MAC normocarbic anesthesia with halothane (N_2 ventilation), CBFc was noted to be 69 ± 23 $\text{ml}\cdot 100\text{g}^{-1}\cdot\text{min}^{-1}$ compared with an isoflurane value of 41 ± 16 $\text{ml}\cdot 100\text{g}^{-1}\cdot\text{min}^{-1}$. This difference was statistically significant, and agrees with the findings of both Drummond et al. (19) and Scheller et al. (23), as well as with the observations made by Todd and Drummond in cats (20) and by Eintrei et al. in humans (24). However, simultaneously recorded CBFss values showed no differences between these volatile agents, i.e., halothane = 71 ± 30 $\text{ml}\cdot 100\text{g}^{-1}\cdot\text{min}^{-1}$, isoflurane = 65 ± 23 $\text{ml}\cdot 100\text{g}^{-1}\cdot\text{min}^{-1}$. If CBFss values are indeed representative of "global" CBF, this suggests that these agents may be producing differing effects on cortical vs. whole brain blood flow, with halothane leading to greater cortical flows. In an experiment directly inspired by this observation, Hansen et al. (25) recently found in rats that halothane appears to increase selectively autoradiographically measured cortical CBF, while having little effect on hemispheric CBF as compared with equi-MAC concentrations of isoflurane. The explanation for this phenomenon remains unclear, but indicates that the regional specificity of any CBF measurement method be carefully considered when examining the effects of anesthetics.

It was found that in rabbits the cerebral effects of N_2O were associated with a variable EEG response, but by a consistent increase in CBF and ICP, regardless of background halothane, isoflurane or fentanyl/pentobarbital anesthesia (although they were attenuated in our fentanyl/pentobarbital animals). These effects were not blocked by hypocarbia, and were not associated with changes in $CMRO_2$. It is not clear whether these observations have any relevance to clinical anesthesia, particularly in view of the small changes in ICP, the apparent species-specificity of the EEG observations, and the long clinical track record of safety of N_2O in neurosurgery. The present observations, however, reconfirm the belief that N_2O has substantial cerebrovascular effects, and hence should not be used in neuroanesthetic practice without first considering such factors.

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Prophylactic Transdermal Scopolamine Patches Reduce Nausea in Postoperative Patients Receiving Epidural Morphine

Keith A. Loper, MD, L. Brian Ready, MD, FRCP(C), and B. Hugh Dorman, MD, PhD

LOPER KA, READY LB, DORMAN BH. Prophylactic transdermal scopolamine patches reduce nausea in postoperative patients receiving epidural morphine. Anesth Analg 1989;68:144–6.

To evaluate the efficacy of prophylactic transdermal scopolamine in reducing nausea associated with postoperative epidural analgesia, we studied 32 healthy adult women undergoing major gynecologic surgery. The patients were randomized in a double blind fashion to receive either a cutaneous scopolamine patch or a visually identical cutaneous placebo patch. Postoperative analgesia was provided solely with epidural morphine. Nausea was treated with metoclopromide and droperidol. At 24 hours postoperatively, the mean nausea score was significantly lower with scopolamine than with placebo (1 ± 2 vs 51 ± 42, respectively, $P < 0.05$). The number of patients reporting "zero nausea" was significantly greater with scopolamine patches than with placebo patches (13 vs 1, $P < 0.01$). The mean number of times antiemetic drugs were administered per patient was lower with scopolamine than with placebo patches (0.2 ± 0.4 vs 2.8 ± 2.6, $P < 0.05$). It is concluded that prophylactic transdermal scopolamine patches reduce nausea in postoperative patients receiving epidural morphine.

Key Words: VOMITING, NAUSEA—postoperative. PARASYMPATHETIC NERVOUS SYSTEM—scopolamine.

Epidural morphine provides excellent analgesia for the management of postoperative pain, but nausea is a commonly reported side effect with an incidence of up to 60% (1). Scopolamine, a belladona alkaloid, is an effective antiemetic when nausea is induced by morphine (2). Bolus administration of scopolamine, however, is associated with a high incidence of dose related adverse effects and has the disadvantage of a short duration of action (2,3).

Transdermal scopolamine patches (Transcope, Ciba) have the advantage of delivering a constant low dosage of drug over a prolonged period. This study evaluates the effectiveness of prophylactic transdermal scopolamine patches in reducing the incidence of nausea in patients receiving epidural morphine following major gynecologic surgery.

Methods

The transdermal system is a laminated structure comprised of an impermeable backing layer, a drug reservoir containing 1.5 mg of scopolamine, a rate controlling microporous membrane, and an adhesive layer. The unit resembles a circular bandaid, 0.2 mm thick and covering an area of 2.5 cm. Placebo units are identical, with the exception that they do not contain scopolamine. The adhesive layer contains 0.14 mg of scopolamine as a priming dose to saturate the skin binding sites and to more rapidly bring the plasma concentration of the drug to steady-state. The system is designed to release scopolamine at a rate of 5 μg/hr over a three-day period.

Following institutional approval and informed consent, 32 healthy women were randomized in a double blind fashion to one of two study groups, each containing 16 subjects. One group received a transdermal scopolamine patch, the other group a placebo patch.

Upon arrival to the surgical holding area, a patch was placed on the skin overlying the right mastoid process. A T4-6 level of epidural anesthesia was established using a lumbar catheter and 2%-lidocaine with epinepherine (1:200,000). If required for the

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Address correspondence and requests for reprints to Dr. Loper, Clinical Pain Service, RC-76, University Hospital, 1959 N.E. Pacific, Seattle, WA 98195.

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Table 1. Variables with Potential Impact on Postoperative Nausea

	Placebo	Scopolamine
Age (years)	46 ± 15	45 ± 15
Weight (kg)	81 ± 30	66 ± 10
Duration of Surgery (minutes)	272 ± 89	217 ± 96
General Anesthesia (cases)	12	14
Morphine Dosage (mg/24 hr)	14 ± 5	13 ± 5

Mean ± S.D., $P > 0.05$.

surgical procedure, general anesthesia was then induced with thiopental, 4–6 mg/kg, and maintained with isoflurane, 0.4–0.9%. Nitrous oxide, atropine, and droperidol were not used. At the end of surgery the epidural catheter was used to administer preservative-free morphine in doses ranging from 3–5 mg. Hence, more than 4 hours elapsed between placement of the cutaneous patch and the epidural administration of narcotic.

Postoperative analgesia was maintained by continued epidural administration of preservative-free morphine, 3–5 mg every 6–12 hours as needed for comfort. No other narcotics or sedatives were administered.

Patients who became nauseated following surgery were treated with metoclopromide, 10 mg IV every two hours for up to four doses. If the nausea persisted, droperidol, 0.625 mg IV every two hours for up to three doses, was given. In patients with intractable nausea at 24 hours postoperatively, the study patch was removed and a patch known to contain scopolamine was placed.

The number of times antiemetic drugs were administered during the initial 24 hours after surgery was recorded. On the first postoperative day, nausea was documented as the nausea score using a 100-mm visual analogue scale, where zero was labeled "no upset stomach" and 100 was labeled "extremely upset stomach." These data were obtained by a blinded observer unaware of the anesthetic management.

Statistical analysis of parametric data was performed utilizing the Chi-squared Test. The Mann-Whitney Test was used for nonparametric data. Statistical significance was assigned at $P < 0.05$.

Results

There were no statistically significant differences with respect to age, weight, anesthetic technique, duration of surgery or epidural morphine dosage in the two groups of patients (Table 1). None of these factors showed a significant correlation with the nausea score.

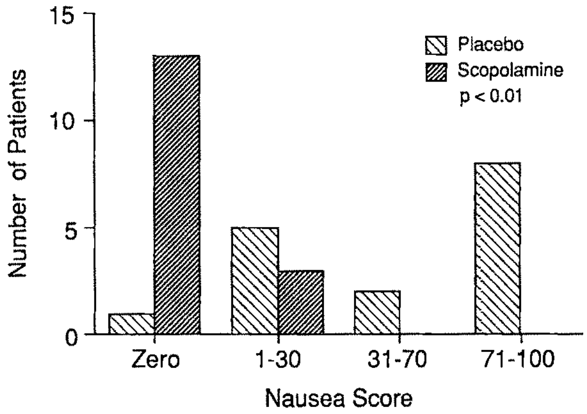

Figure 1. Distribution of visual analog nausea scores.

There was a significant difference between the scopolamine and placebo groups with respect to both the incidence and severity of nausea (Fig. 1). Further, the mean number of times antiemetic drugs were administered per patient was lower in the scopolamine group than in the placebo group (2.8 ± 2.6 vs 0.2 ± 0.4, $P < 0.05$).

Of note, seven of the eight patients in the placebo group with intractable nausea had resolution of their nausea within 4–6 hours of treatment with a scopolamine patch.

Discussion

Our goal was to evaluate the efficacy of prophylactic transdermal scopolamine patches as a means of reducing the nausea associated with epidurally administered morphine. Opiates are usually thought to induce nausea by direct stimulation of the chemotactic trigger zone. It has, however, also been suggested that opiates may sensitize the vestibular system to motion and thereby induce nausea (6). Hence, patients given epidural morphine may complain that nausea is exacerbated by moving their head or changing the visual point of reference. Transdermal scopolamine is highly effective in the prophylaxis and treatment of motion sickness (4,5).

Our study demonstrated that the prophylactic use of transdermal scopolamine patches significantly reduces the incidence and severity of nausea associated with epidural morphine in postoperative gynecologic patients. A previous report (in abstract form) found that transdermal scopolamine patches did not induce cycloplegia, confusion, psychomimetic reactions or other disturbing behavior in postoperative patients (7). While in that study transdermal scopolamine patches tended to reduce the incidence of nausea, the reduction was not statistically significant. Similar findings were reported by Uppington et al. in a study involving postoperative gynecologic patients (8). In both these studies all patients received atropine, a known antiemetic, and nitrous oxide, which is suspected of increasing the incidence of postoperative nausea (9,10). Our study eliminated these confounding factors by selecting one surgical population, proscibing the use of atropine, nitrous oxide and parenteral narcotics, and managing postoperative pain solely with epidural morphine.

The effectiveness of scopolamine was further demonstrated in the seven patients whose nausea resolved with the transderm scopolamine, having previously failed to respond to both metoclopromide and droperidol. While we did not measure cycloplegia or dry mouth, we did not experience any problems involving urinary retention or psycomimetic reactions.

Correct placement of a transdermal scopolamine patch on the skin over the mastoid process is important as this area is favorable to the absorption of scopolamine. By comparison, the postauricular skin is 10 times more permeable than that of the thigh (11). For prophylactic use, the patch should be placed on the skin at least 4 to 6 hours before the antiemetic effect is required. Transdermal scopolamine patches are not recommended for use in patients with glaucoma, intestinal obstruction or urinary bladder neck obstruction (12).

We found that, in patients receiving epidural morphine following major gynecologic surgery, transdermal scopolamine patches significantly reduce the incidence and severity of nausea.

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Metabolism of I-653 and Isoflurane in Swine

Donald D. Koblin, PhD, MD, Richard B. Weiskopf, MD, Margot A. Holmes, BS, Krystyna Konopka, PhD, MD, Ira J. Rampil, MD, Edmond I. Eger, II, MD, and Lucy Waskell, MD, PhD

Fluoride ion concentrations were measured in plasma samples taken from chronically instrumented domestic swine before, immediately after, and 4 hours after exposure to either I-653 or isoflurane. Each anesthetic was administered at concentrations between 0.7 and 1.6 MAC and the total dose of anesthetic given was approximately 5.5 MAC hours for each agent. Plasma fluoride ion concentrations immediately after and 4 hours after exposure to isoflurane were approximately three times greater than values obtained in awake swine before anesthesia. In contrast, swine given I-653 had no detectable elevation in plasma fluoride concentration immediately after anesthesia, but a 17% ($P < 0.05$) increase in plasma fluoride ion concentration 4 hours after anesthesia. These results imply that I-653 is metabolized less than is isoflurane in swine.

Key Words: ANESTHETICS, VOLATILE: I-653, isoflurane. BIOTRANSFORMATION, DRUG—I-653, isoflurane.

I-653 ($CF_2H\text{-}O\text{-}CFH\text{-}CF_3$) is a new volatile anesthetic that allows a rapid induction of anesthesia and an awakening time (in rats) that is three to five times faster than isoflurane (1,2). Thus, I-653 may prove to be a clinically useful agent when a rapid onset and recovery from anesthesia are desired. Another desirable feature of I-653 appears to be its resistance to biodegradation. We have shown in previous studies that enzyme-induced rats minimally metabolize I-653 (3) and that I-653 does not cause hepatic injury in hypoxic enzyme-induced rats (4) or rats anesthetized repeatedly (5). However, marked species differences may exist in drug metabolism research (6). The rat, although perhaps the most commonly employed species in drug metabolism research, is deficient in overall drug metabolizing activity when compared to other species (7). During a recent series of studies that analyzed the cardiovascular effects of I-653 in swine (8), we had the opportunity to assess the metabolism of I-653 in swine, using the appearance of fluoride ion in the plasma after exposure as an index of anesthetic metabolism. We compared these fluoride ion concentrations with those from the same swine when they were given isoflurane.

Materials and Methods

Animals

This study was approved by the UCSF Committee on Animal Research. Eight domestic female swine weighing 17.0 + 6.8 kg (±SD) were anesthetized with halothane and instrumented with chronically indwelling lumbar aortic and thermodilution pulmonary arterial cannulae as previously described (8). Three to 7 days after placement of the cannulae, a heparinized arterial blood sample (approximately 2 ml) was obtained from each conscious pig. Swine were then given either I-653 or isoflurane in oxygen (in random order) at anesthetic concentrations of 0.8 to 1.6 minimum alveolar concentration (MAC) for I-653 and 0.7 to 1.4 MAC for isoflurane, and the cardiorespiratory effects of I-653 or isoflurane were evaluated (8). Swine were 63 to 84 days old at the time of exposure to I-653 or isoflurane. Three to 8 days later, an arterial blood sample was again obtained from each conscious pig before administration of the alternate anesthetic. The swine were maintained normothermic at a mean pulmonary artery temperature of 38.9°C throughout

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Address correspondence to Dr. Koblin, Anesthesiology Service (129), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, CA 94121.

anesthesia. At this temperature, MAC obtained by clamping the dew claw is 10.0% for I-653 and 2.04% for isoflurane (9). The total dose of I-653 administered was 5.4 ± 0.3 (±SD) MAC hours and that for isoflurane was 5.5 ± 1.0 (±SD) MAC hours. The swine received no medications except the inhaled agents, succinylcholine (2 mg/kg) given to facilitate intubation, and epinephrine given to test for sensitization of the myocardium. Immediately after discontinuation of the anesthetic, and 4 hours later, arterial blood samples were obtained and analyzed for plasma fluoride ion concentrations.

Fluoride Analyses

Plasma was isolated from arterial blood samples by centrifugation at 1000 *g* for 10 min. Plasma samples were maintained at −20 to −30°C before analysis. Fluoride ion concentrations were determined with a modified method of Fry and Taves (10). Thawed plasma samples were centrifuged at 10,000 *g* for 3 min to remove particulate material. Twenty μl of a 5 M sodium acetate buffer (pH 4.5) was added to 180 μl of undiluted plasma. The 200-μl mixture was placed in a machined Teflon cup and fluoride ion concentration was measured using an Orion fluoride ion electrode (model 96-09) with either a Corning model 12 pH meter or a Corning 150 ion analyzer. Fluoride ion concentrations in plasma were obtained by interpolation with a calibration curve prepared by a semilogarithmic plot of the instrument voltage output versus the concentration of sodium fluoride. This plot was linear over the range of fluoride ion concentrations measured in this study (0.65 to 5.5 μM). Sensitivity of the method was approximately 0.1 μM.

Statistical comparisons were made between fluoride ion concentrations in the awake state and those present immediately after and 4 hours after discontinuation of the anesthetic. Computations were performed with a paired *t*-test using the Bonferroni correction for multiple comparisons. *P* values of <0.05 were considered statistically significant.

Results

Plasma fluoride ion concentrations in swine given isoflurane were approximately three times those measured in conscious pigs before isoflurane exposure ($P < 0.001$). This increase was found both at the end of anesthesia and 4 hours later (Table 1). In contrast, no significant increase in plasma fluoride ion concentration was detected immediately after I-653 administration. However, plasma fluoride concentrations increased slightly (17%; $P < 0.05$) 4 hours later (Table 1).

Table 1. Plasma Concentrations of Fluoride Ion (μM)*

Time	Anesthetic	
	I-653	Isoflurane
Before anesthesia	1.29 ± 0.37	1.15 ± 0.37
End of anesthesia	1.32 ± 0.40	3.44 ± 1.06‡
4 Hours after anesthesia	1.51 ± 0.36†	3.75 ± 0.35‡

*Mean values ± SD taken from eight swine in the I-653 group and seven in the isoflurane group.

†$P < 0.05$.

‡$P < 0.001$ when compared to awake swine before anesthesia.

Arterial blood samples were not obtained in one pig anesthetized with isoflurane. Thus, the number of pigs in the isoflurane-exposed group is one less than the number in the I-653–exposed group.

Discussion

The present results in swine are consistent with the results obtained in another species, rats (3), and suggest that I-653 is minimally biotransformed by intact animals. The previous studies maximized metabolic breakdown of I-653 by providing rats with drinking solutions containing phenobarbital or ethanol to promote enzyme induction (3). With one exception (a slight increase in serum fluoride ion at the termination of anesthesia in phenobarbital-pretreated rats), no increases in serum and urine fluoride ion concentrations were detected in I-653-exposed compared to control rats. However, significant increases in the excretion of urinary organic fluoride were found in the I-653-exposed rats that were pretreated with ethanol or phenobarbital (3). In animals that were not enzyme-induced, the previous rat studies (3) did not reveal any elevation in serum fluoride ion after exposure to I-653, whereas a statistically significant 17% increase in the concentration of plasma fluoride ion was found 4 hours after swine were exposed to I-653 (Table 1). This increase was approximately a twelfth of that found with isoflurane.

Although hepatic enzymes were not deliberately induced in the present study, some induction may have occurred because of the anesthesia required for catheter placements. This anesthesia usually required halothane (used as a control for arrhythmogenic studies). Increased hepatic microsomal activity after halothane anesthesia in children may last for 4 days after anesthesia and surgery (11). Similarly, some degree of enzyme-induction may have followed the first of the two anesthesias in which plasma fluoride concentrations were measured (i.e., the second exposure may have been in an enzyme-induced animal). Although rats exposed to 0.3% isoflurane for 7 hrs have a reduced hexobarbital sleeping time 1 day after exposure (12), intermittent exposure to isoflurane for 9 weeks does not alter the level of hepatic cytochrome P-450 in rats (13). However, enzyme induction seems unlikely in the present experiments because plasma fluoride ion concentrations did not differ in the two groups of conscious animals given I-653 or isoflurane (Table 1).

In the present experiments, plasma fluoride levels were employed as indicators of the biodegradation of I-653 and isoflurane. The assumption was made that the greater the plasma fluoride concentration, the greater the extent of anesthetic metabolism. Although this is probably a reasonable assumption, it remains possible that anesthetic breakdown could occur without the production of fluoride ion or that once fluoride ion was generated it could be sequestered by tissue (e.g., bone) and not appear in blood.

The peak plasma fluoride ion concentration in swine exposed to 5.5 MAC hours of isoflurane was approximately 4 μM. Similar fluoride ion levels were obtained immediately on termination of the anesthetic and 4 hours later. This value is similar to the peak serum fluoride ion concentration observed 6 hours after anesthesia in patients given isoflurane for 3 MAC hours (14). In phenobarbital-induced rats exposed to 1.6 MAC isoflurane or I-653 for 2 hours, peak serum fluoride ion concentrations were found for both anesthetics immediately after anesthetic exposure, with fluoride ion levels declining steadily thereafter (3). In the present studies in swine, it would seem reasonable to expect the peak plasma fluoride ion concentrations to be achieved within several hours after anesthesia, especially for the poorly soluble I-653, which undergoes an extremely rapid elimination. It remains possible that slightly higher plasma fluoride ion concentrations might have been observed if additional measurements had been performed at times between 0 to 4 hours or >4 hours after anesthesia. Although the relative concentration of plasma fluoride ion was greater after anesthesia with isoflurane than after I-653 (Table 1), the peak fluoride concentrations attained with both anesthetics were substantially lower than those (approximately 35 μM) that cause subclinical renal toxicity (15).

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The Arterial Pressure Waveform During Acute Ventricular Failure and Synchronized External Chest Compression

Reuven Pizov, MD, Yosef Ya'ari, MD, and Azriel Perel, MD

PIZOV R, YA'ARI Y, PEREL A. The arterial pressure waveform during acute ventricular failure and synchronized external chest compression. Anesth Analg 1989;68:150–6.

Methods for mechanical cardiac support by intermittent increases in the intrathoracic pressure have recently been described. In the present study the responses of the arterial pressure waveform to mechanical ventilation with and without synchronized external chest compression (SEC) in the presence of acute ventricular failure (AVF) were evaluated by measuring the systolic pressure variation (SPV). SPV, the difference between the maximal and minimal values of systolic blood during a single positive pressure breath, consists of Δup and Δdown components when systolic blood pressure during a short apnea is used as reference value. During intermittent positive pressure ventilation (IPPV) alone, AVF caused SPV to decrease significantly from 8.8 ± 4.0 to 5.7 ± 1.9 mm Hg, and further to 3.1 ± 1.1 mm Hg after volume loading ($P < 0.02$). The decrease in SPV was due to a significant decrease in the Δdown component, whereas the Δup became the major component of the reduced SPV. The application of SEC caused significant increases in the Δdown, Δup, and overall SPV during AVF without volume loading. However, during AVF with volume loading, SEC increased only the Δup component of the SPV, signifying a transient increase in the left ventricular stroke output. It is concluded that the disappearance of the Δdown component of the SPV is characteristic of congestive heart failure. Analysis of the arterial waveform offers a readily available monitoring tool for the differentiation of the possible effects on increased intrathoracic pressure. The appearance of a prominent Δdown signifies inadequate preload and possible reduction in cardiac output, whereas a significant Δup component is the reflection of a true mechanical cardiac support.

Key Words: BLOOD PRESSURE, ARTERIAL—waveform. VENTILATION, ARTIFICIAL—vascular effects.

The effect of intermittent positive pressure ventilation (IPPV) on the circulation is variable. Frequently, the increase in intrathoracic pressure during IPPV reduces cardiac output (CO) because of the associated decrease in venous return (1,2). In other circumstances, such as cardiac dysfunction, IPPV may improve cardiac output (3,4). Indeed, techniques that use intermittent increases in intrathoracic pressure have been recently employed to improve cardiac function during acute ventricular failure (AVF) (5–9). Such techniques, though, necessitate careful patient selection as well as careful monitoring of their effects on the circulation (10).

We have previously described (11) the effects of hypovolemia on systolic pressure variation (SPV), which is the difference between maximal and minimal values of systolic blood pressure during one mechanical breath. The SPV can be further divided into Δup and Δdown components, by using the systolic blood pressure after a short apnea as a reference value (Fig. 1). The Δdown component of the SPV reflects the decrease in the left ventricular stroke output due to reduced preload after the increase in intrathoracic pressure (2,12). The Δup represents a transient increase in the left ventricular stroke output due to increased filling of the left ventricle by squeezing the blood out of the pulmonary vascular bed, and due to the reduction in the left ventricular effective afterload (13–16). We have described the value of the SPV in detecting occult hypovolemia during graded hemorrhage (11) and in differentiating normovolemic and hypovolemic hypotension (17).

In the present study we have used such analysis to examine the effects of external chest wall compres-

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Address correspondence to Dr. Pizov, Department of Anesthesiology, Hadassah University Hospital, Ein Kerem POB 12000, Jerusalem 91120, Israel.

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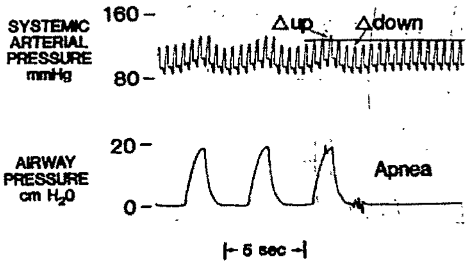

Figure 1. Principles of arterial waveform analysis: the systolic pressure variation (SPV) and its Δup and Δdown components. The Δup and Δdown are measured relative to systolic blood pressure during apnea.

sion synchronized with IPPV in a model of acute ventricular failure in dogs. We have tried to answer the following questions: 1) What are the effects of acute ventricular failure (AVF) on SPV? and 2) Are the hemodynamic effects of synchronized external chest compression (SEC) reflected in the arterial pressure waveform?

Methods

Ten dogs weighing 18.6 ± 2.5 kg (mean ± SD) were anesthetized with intravenous (IV) pentobarbital (30 mg/kg), intubated with an endotracheal tube, and paralyzed by a continuous IV infusion of succinylcholine ($0.01\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The dogs were ventilated by a Mark 8 Bird respirator with a constant tidal volume of 15 ml/kg at a rate of 15 breaths/min, (mean Pa_{CO_2} 34.4 ± 6.8 mm Hg) and an FI_{O_2} of 0.3–0.6 with 0.5% halothane. Occasional baseline metabolic acidosis was corrected with sodium bicarbonate. Throughout the preparation each dog received a total of 5 ml/mg Hemaccel (3.5% colloidal gelatin solution (Behring, Behringwerke AG, Marburg, West Germany) to avoid inadvertent hypovolemia.

A 16-g Teflon catheter was inserted into the femoral artery, and a pulmonary arterial catheter (7F, Instrumentation Laboratories, Lexington, Massachusetts) was floated through the external jugular vein. An 8F catheter with additional side holes was inserted into the pleural space through the fifth intercostal space at the right midaxillary line for measurement of pleural pressure (Ppl). Airway pressure was measured through an opening in the endotracheal tube close to its tip. The airway and pleural pressure lines were filled with normal saline and connected to Statham P23Db transducers. In six dogs, an 8F femoral-ventricular pigtail catheter (Cordis Corporation, Miami) was introduced into the left ventricle through the left femoral artery to evaluate the degree of myocardial depression. The vascular catheters were connected to Bentley Trantec model 800 transducers (Bentley Lab) and all pressure traces were continuously recorded on a Hewlett-Packard recorder (7788A). The left ventricular pressure signal was differentiated (dP/dt) using an HP 8805B amplifier. Left ventricular end-diastolic (LVEDP_t) and peak systolic (LVPSP_t) transmural pressures were calculated by subtracting Ppl from corresponding intraventricular pressures.

Cardiac output was measured in triplicate by the injection of 5 ml iced saline using IL cardiac output computer (model 701, Lexington, Massachusetts). All injections were performed during early expiration. Systemic (SVR) and pulmonary (PVR) vascular resistances, as well as intrapulmonary right-to-left shunt (Qs/Qt) were calculated using standard formulas.

Systolic pressure variation was measured as the mean difference between the maximal and minimal systolic blood pressure (SBP) during five consecutive breaths. The Δup and Δdown components of the SPV were measured relative to the SBP during 5 seconds of apnea (SBP apn) (Fig. 1). After baseline data were recorded, acute ventricular failure (AVF) was induced by graded intravenous administration of sodium pentobarbital and 0.05 mg/kg methoxamine followed by a constant infusion of pentobarbital ($0.3\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and methoxamine ($0.5\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Initial pentobarbital administration was done in 10-mg/kg increments at 10-minute intervals until a relatively stable decrease of about 50% in cardiac output (CO) was achieved.

Synchronized external compression of the chest was achieved by the intermittent inflation of an inflatable 15-cm wide vest that was applied around the dogs' chest. The vest was applied so as not to cause any increase in the end-expiratory Ppl, which remained subatmospheric. Vest inflation was timed to occur during mechanical inspiration by synchronization of flow delivery to the ventilator and the perithoracic vest. The amount of vest inflation was adjusted by a flowmeter so as to produce the desired increase in pleural pressure during each breath. Tidal volumes remained constant during SEC.

After the induction of the first stage of AVF (AVF_1), SEC was started so that the change in Ppl with each breath was 10 mm Hg. After 15 minutes, SEC was increased to produce a ΔPpl of 15 mm Hg for another 15 minutes. Synchronized external chest compression was then stopped and Hemaccel (984 ± 397 ml) was infused for about 30 minutes until pulmonary capillary wedge pressure (PCWP) reached 20 mm Hg. This stage of AVF with volume loading was termed AVF_2. All measurements were repeated again during IPPV alone, and during IPPV with SEC that produced ΔPpl of 10 (SEC 10) and ΔPpl of 15 mm Hg (SEC 15), each stage lasting 15 minutes.

Table 1. The Effects of Synchronized External Compression (SEC) to aΔP_{pl} of 10 (SEC 10) and 15 (SEC 15) mm Hg during Acute Ventricular Failure without (AVF_1) and with (AVF_2) Volume Loading

		AVF_1			AVF_2		
	Baseline	IPPV	SEC 10	SEC 15	IPPV	SEC 10	SEC 15
CO (L/min)	3.11 ± 0.78	1.57 ± 0.39†	1.32 ± 0.39‡	1.29 ± 0.53‡	2.84 ± 1.38	2.65 ± 1.11	2.61 ± 1.2§
HR (beats/min)	159 ± 22	120 ± 10†	116 ± 12‡	116 ± 13‡	116 ± 16†	111 ± 18†	110 ± 17‡
MBP (mm Hg)	111 ± 20	69 ± 21†	65 ± 21‡	63 ± 28	97 ± 29	94 ± 29	93 ± 31§
CVP (mm Hg)	1.6 ± 1.2	4.4 ± 1.8†	5.4 ± 2.4	5.5 ± 2.9	13.5 ± 3.4†	13.8 ± 3.5	13.5 ± 3.2§
MPAP (mm Hg)	14.7 ± 3.2	14.2 ± 3.3	13.9 ± 2.7	13.8 ± 3.7	27.2 ± 3.0†	27.1 ± 2.3	25.6 ± 3.4‡,§
PCWP (mm Hg)	5.1 ± 3.1	7.2 ± 2.8	7.5 ± 2.3	7.8 ± 2.6	19.4 ± 1.1†	19.3 ± 0.7	18.0 ± 1.8‡,§
P_{aw} (mm Hg)	7.2 ± 1.8	7.7 ± 1.3	18.3 ± 5.5‡	26.4 ± 8.2‡	12.1 ± 3.8†	19.4 ± 4.5†	26.7 ± 3.5‡
ΔP_{pl} (mm Hg)	3.0 ± 1.0	3.4 ± 0.9	10.2 ± 0.6‡	15.9 ± 2.4‡	4.5 ± 1.4†	10.2 ± 0.6†	16.7 ± 2.2‡
$LVEDP_t$* (mm Hg)	9.5 ± 1.9	12.7 ± 3.9	12.3 ± 2.9	11.2 ± 2.2	25.5 ± 10.3†	25.2 ± 9.6	24.0 ± 8.4§
$LVPSP_t$* (mm Hg)	138 ± 28	97 ± 27	89 ± 25‡	82 ± 28‡	141 ± 29	139 ± 32	138 ± 31§
dP/dt* (mm Hg/sec)	2497 ± 997	832 ± 486†	773 ± 432	682 ± 397‡	1444 ± 652†	1445 ± 698	1438 ± 795§
Qs/Qt (%)	8.7 ± 2.6	5.7 ± 2.9	9.2 ± 6.3	9.4 ± 5.5	18.8 ± 13.1	20.3 ± 12.7	23.7 ± 12.7§
SVR (dynes·sec/cm^5)	2982 ± 851	3416 ± 1327	3805 ± 1601	3729 ± 1741	2658 ± 1254	2656 ± 1162	2586 ± 1008§
PVR (dynes·sec/cm^5)	262 ± 86	363 ± 78	400 ± 99	432 ± 169	253 ± 90	268 ± 110	269 ± 134§

Abbreviations: aΔP_{pl}, change in pleural pressure in each breath; IPPV, intermittent positive pressure ventilation; CO, cardiac output; HR, heart rate; MBP, mean blood pressure; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; P_{aw}, peak airway pressure; $LVEDP_t$, left ventricular end-diastolic transmural pressure; $LVPSP_t$, left ventricular peak systolic transmural pressure; dP/dt, Qs/Qt, intrapulmonary right-to-left shunt; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

*$n = 6$; †$P < 0.05$ compared with baseline; ‡$P < 0.05$ compared with IPPV without SEC; §$P < 0.05$ compared with SEC 15 during AVF_1.

Statistical Methods

We compared the values measured at AVF_1 and AVF_2 with baseline values using the Wilcoxon matched-pairs test. We also compared the measurements obtained at SEC 10 and SEC 15 with the corresponding AVF stage without SEC. Values at SEC 15 were compared between AVF_1 and AVF_2 using the same statistical method. $P < 0.05$ was considered to be statistically significant. All values are shown as mean ± SD.

Results

Effects of Acute Ventricular Failure on the Arterial Waveform

The induction of acute ventricular failure (AVF_1) caused a decrease in the CO, mean blood pressure (MBP), and dP/dt (Table 1). Filling pressures were somewhat elevated, although only the cardiac ventricular pressure (CVP) increased significantly (Table 1).

When AVF was combined with volume loading, (i.e., AVF_2), $LVEDP_t$, CVP, and PCWP increased significantly compared with the control state. Cardiac output and MBP returned close to baseline values, while the dP/dt, although improved, was still significantly lower than the control state.

During AVF_1 and AVF_2, the SPV decreased to 5.7 ± 1.9 and 3.1 ± 1.1 mm Hg, respectively, compared with a baseline value of 8.8 ± 4.0 ($P < 0.02$) (Fig. 2, 3). The decrease in the SPV was due to a significant decrease in the Δdown component from 9.1 ± 5.3 to 3.8 ± 1.8 mm Hg during AVF_1 and to 0.4 ± 0.5 mm Hg during AVF_2 ($P < 0.02$). The Δup at AVF_2 (2.7 ± 1.3 mm Hg) was significantly above baseline values (−0.2 ± 2.3 mm Hg; $P < 0.02$).

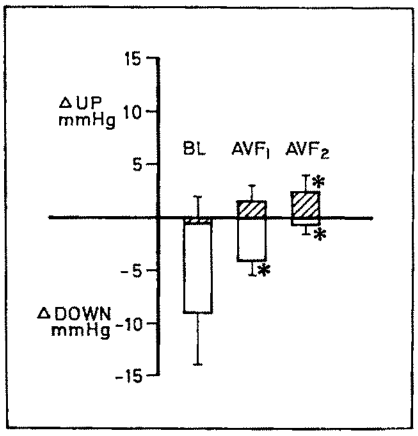

Figure 2. The effects of acute ventricular failure without (AVF_1) and with (AVF_2) volume loading in the arterial waveform. Note that the Δup and Δdown constitute the SPV. $^*P < 0.05$ compared with baseline (BL).

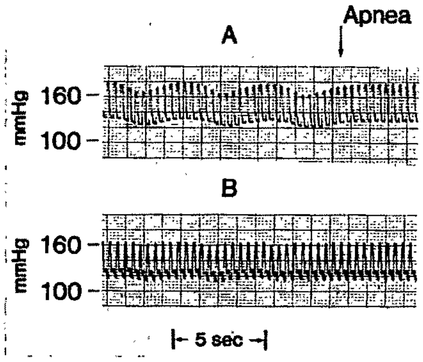

Figure 3. Normal arterial waveform (A) and the arterial waveform after induction of acute ventricular failure and volume loading (B) in the same dog. Note the nearly complete disappearance of the systolic pressure variation.

Effects of Synchronized External Compression during Acute Ventricular Failure

Synchronized external compression during AVF_1 decreased cardiac output from 1.57 ± 0.39 to 1.32 ± 0.39 L/min at SEC 10 ($P < 0.01$), and to 1.29 ± 0.53 L/min at SEC 15 ($P < 0.01$), while filling pressures remained unchanged (Table 1). When SEC was applied during AVF_2, CO, MBP, and filling pressures did not change compared with their baseline values.

During AVF_1, SEC of 10 and 15 significantly increased SPV from 5.7 ± 1.9 to 13.5 ± 3.8 and 20.1 ± 6.9 mm Hg, respectively. This was due to separate significant increases in both the Δup and Δdown components (Fig. 4, 5). During AVF_2, SEC of 10 and 15 increased SPV from 3.1 ± 1.1 to 8.6 ± 2.9 and 14.7 ± 4.5 mm Hg, respectively ($P < 0.01$). However, these increases were due mainly to higher Δup values, while Δdown was practically unchanged (Fig. 4, 5). At SEC 15, the Δdown during AVF_1 was 8.8 ± 5.5 mm Hg, while during AVF_2 the Δdown also at SEC 15 was only 1.9 ± 1.7 ($P < 0.05$).

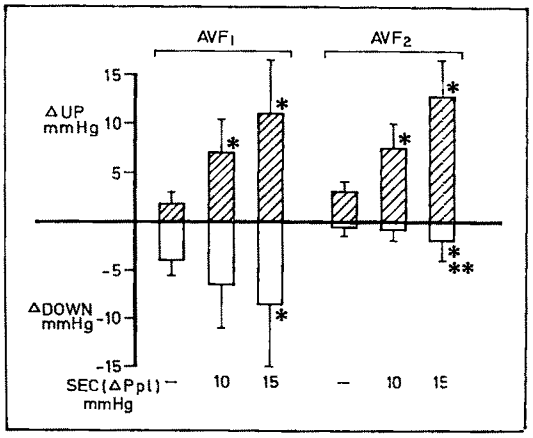

Figure 4. The effects of synchronized external compression (SEC) to a ΔPpl of 10 and 15 mm Hg on the arterial waveform during acute ventricular failure (AVF). AVF_1, without volume loading; AVF_2, with volume loading. Note that the Δup and Δdown constitute the SPV. $^*P < 0.05$ compared with IPPV without SEC; $^{**}P < 0.01$ compared to SEC 15 during AVF.

Discussion

The Arterial Waveform during Acute Ventricular Failure

Analysis of the effects of IPPV on the arterial waveform was shown in our previous studies (11,17) to offer additional hemodynamic information during conditions in which preload was compromised by various mechanisms. In a model of graded moderate hypovolemia, we found systolic pressure variation (SPV) to be a sensitive indicator of the volume status that correlated with the degree of hypovolemia as well as the cardiac output, and did so better than other commonly measured variables (11). We further found that SPV was significantly higher during hemorrhage-induced hypotension than during the same level of hypotension induced by sodium nitroprusside (17).

The SPV during inadequate preload states is composed mainly of the Δdown fraction; that is, the systolic pressure decreases significantly after each breath. The increased Δdown fraction reflects transient reduction in the left ventricular stroke output due to decrease in the already compromised venous return. The transiently reduced venous return appears as a decrease in the blood pressure after a lag time due to the passage through the pulmonary circulation and left side of the heart. Thus the variation in systolic blood pressure may serve as a quantifiable useful clinical variable that detects hypovole-

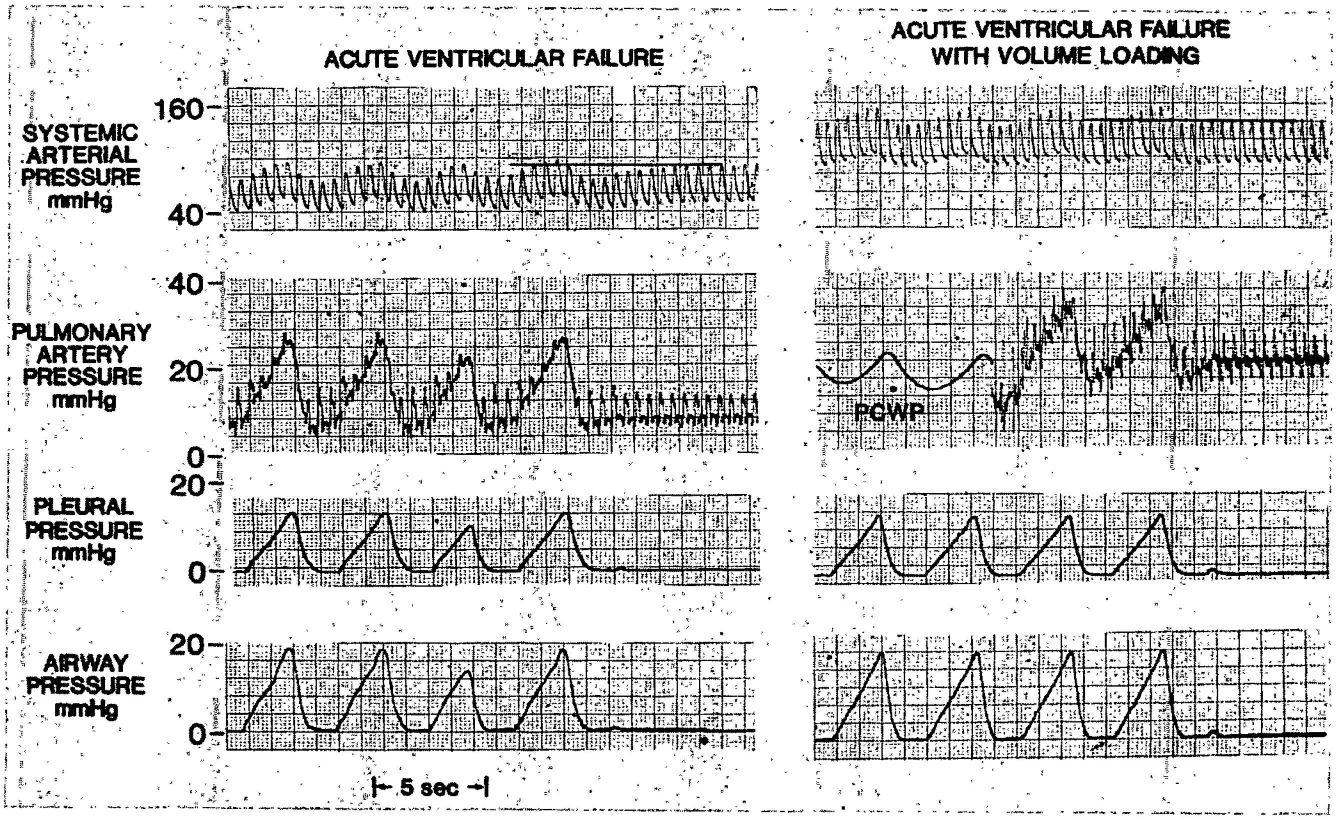

Figure 5. The effect of IPPV with synchronized external compression (SEC) during acute ventricular failure without (AVF_1) and with (AVF_2) volume loading. The systolic pressure variation during AVF_1 is composed mainly of the Δdown, while during AVF_2 the SPV is composed mainly of the Δup component. The line denoting systolic pressure during apnea serves as a reference for dividing SPV into Δup and Δdown.

mia by the response of the blood pressure to an increase in intrathoracic pressure.

In this study we attempted to see whether during acute ventricular failure SPV has distinct features that may be clinically useful. The most striking finding was the diminution of the Δdown component once AVF was induced. Indeed, the Δdown virtually disappeared during AVF_2, i.e., when AVF was combined with volume loading so as to resemble a state of congestive heart failure. The disappearance of the normal decrease in blood pressure after a mechanical breath reflects the relative independence of the left ventricular output from changes in preload during CHF. The congested heart does not reduce its output in response to reduced preload and, in fact, most of our therapeutic approaches to patients in CHF are aimed at preload reduction.

It seems then that during a low-flow state, the lack of a significant Δdown in the arterial waveform is suggestive of ventricular failure, while a prominent Δdown will be indicative of hypovolemia. However, in noncongestive ventricular failure, the Δdown may still be significant and the cardiac output may respond to volume loading as shown in the improvement seen in our model between AVF_1 and AVF_2.

While the Δdown becomes less significant during AVF, the Δup component becomes more prominent. The Δup reflects a normally present transient increase in the left ventricular stroke output at the beginning of mechanical inspiration. Such an increase was first reported in 1973 by Massumi et al. (18), who termed it "reversed pulsus paradoxus." Since then it has been shown that an increase in airway pressure augments the left ventricular stroke output by increasing preload to the left ventricle due to increased pulmonary venous return (13). In addition, the afterload of the left ventricle is reduced due to an increase of the gradient between thoracic to abdominal pressure gradient and to direct pressure of the lungs on the heart (14–16). Improved left ventricular compliance due to transient reduction of the right heart volume may also play a role in the improved left ventricular ejection during mechanical inspiration (14).

In our model the ratio of Δup/Δdown increased from <5% during the baseline state in an anesthetized dog to 50% during AVF_1, and to 680% (!) during AVF_2. Thus, the Δup is the more prominent component of the SPV during AVF, especially when the latter is accompanied by hypervolemia. The mechanism by which IPPV produces augmentation in the left ventricular (LV) stroke output was further explored when SEC was applied.

The Effects of Synchronized External Compression on Hemodynamics and on the Arterial Waveform

In recent years it has repeatedly been shown (3,4) that in certain clinical conditions, IPPV may actually improve cardiac function. Intermittent increases in intrathoracic pressure may improve left ventricular function by reducing afterload (16) and in an asystolic patient can produce a pressure gradient between the thoracic and systemic vascular systems, generating forward blood flow (15). Pinsky et al. (5–9), for example, found that increased intrathoracic pressure generated by IPPV or high-frequency jet ventilation (HFJV) improved cardiac performance in both a canine model of AVF (5–7) and in patients with cardiac failure (8,9). In the latter, binders were applied around the chest wall of the patients so as to reduce chest wall compliance, increase airway pressure during inspiration, and thus improve left ventricular ejection. It was further shown that where the increase in airway pressure is timed to occur at late systole, the resultant stroke output augmentation is optimal, and may be compared to the effect of the intra-aortic balloon (6,9).

In our model of AVF we have tried to assist left heart function by inflation of a perithoracic vest in synchrony with a conventional mechanical inspiration. Such an approach has been tried before as a technique for cardiopulmonary resuscitation (19), but has not been used during AVF. Our results failed to show an increase in the CO as measured by thermodilution. In fact, during AVF_1, i.e., ventricular failure without volume loading, SEC actually decreased cardiac output. This negative effect of SEC was reflected in the significant increase in the Δdown component of SPV, denoting considerable reduction in the venous return in response to the high level of airway pressure used. Other investigators (7) have also found the expected augmentation of cardiac function to be limited by inadequate preload. Indeed, in a recent editorial (10), the need for careful selection of patients and the establishment of preload independence were mentioned as prerequisites before use of any such cardiac support is attempted. From our results it seems that the appearance of a significant Δdown in the arterial waveform once SEC is applied is the best indicator of such insufficient preload. Before total cardiovascular deterioration occurs, such preload inadequacy cannot be foreseen from following absolute levels of filling pressures alone.

There are some possible explanations for the lack of improvement in CO in response to SEC in our model. We have not used abdominal binders, contrary to the previously described model, although we achieved similar levels of intrathoracic pressure (5,7). We also used a relatively slow respiratory rate that may have been insufficient to produce an overall improvement in CO. The presence of a Δup component was, however, indicative of a transient increase in cardiac output. This was also verified in a few experiments in which a flowmeter probe (Carolina Medical Electronics) was put around the carotid or femoral arteries and showed transient increases in arterial blood flow corresponding to the Δup component in the arterial pressure waveform. There was some increase in left ventricular stroke output in response to SEC, but this increase did not change overall cardiac output to any significant degree. In this regard it is important to remember that the thermodilution technique may produce inaccurate CO results due to IPPV-induced variations in the right ventricular stroke output (20).

There are three possible mechanisms for the increased left ventricular stroke output during SEC. The first is augmentation of the left ventricular preload due to squeezing of pulmonary blood from the lungs and into the left atrium. This is probably the main mechanism responsible for the Δup fraction in the normal arterial waveform. However, the contribution of this increase in preload to the output of a failing congested heart may be extremely variable. The second possible mechanism is improvement in myocardial contractility due to improved compliance of the left ventricle as the right ventricle volume decreases with inspiration (13,14). Other investigators (16,21) have not found the velocity of myocardial shortening and left ventricular dP/dt to change with increases in intrathoracic pressure. Likewise, we have not found SEC to change the dP/dt, nor was there a difference in the dP/dt of high and low stroke outputs. The third explanation for the increased Δup during SEC is a transient reduction in LV afterload leading to a better LV ejection (14,16). We have found the increases in the systolic pressure to be unaccompanied by similar increases in the left ventricular transmural systolic pressure, which remained unchanged throughout the respiratory cycle even during SEC. Thus, with the same left ventricular systolic wall stress following mechanical inspiration, higher systolic peripheral pressures were achieved due to higher ventricular stroke outputs. These results correspond with previous observations that reduced transmural aortic impedance follows cardiac cycle-specific increases in the intrathoracic pressure (6).

In conclusion, the overall effects of SEC during AVF depend on a number of factors, of which the status of the preload is crucial. Inadequate preload may result in severe reduction in venous return and hence decrease in the cardiac output after SEC. When preload is adequate, the beneficial effects of SEC depend on the amount and timing of the increase in the intrathoracic pressure. Analysis of the arterial waveform offers a readily available monitoring tool for the differentiation of the possible effects of any method for mechanical cardiac support using increased intrathoracic pressure. Furthermore, our findings suggest that the systolic pressure variation may offer important information as to the nature of low-flow states in general. Specifically, the Δdown component will be prominent during hypovolemia, and practically nonexistent during congestive heart failure.

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The Lumbar Epidural Space in Patients Examined with Epiduroscopy

Rune G. Blomberg, MD, and Sven S. Olsson, MD

BLOMBERG RG, OLSSON SS. The lumbar epidural space in patients examined with epiduroscopy. Anesth Analg 1989;68:157–60.

Percutaneous epiduroscopy was performed in 10 patients with the aim of comparing the lumbar epidural space of the patients with the findings made earlier in autopsy subjects. The patients were scheduled for partial laminectomy for a herniated lumbar disc. A complete examination was possible in eight subjects. The extent of view was very limited. The epidural space opened up only temporarily as air was injected. The dura mater lay very close to the dorsal aspect of the epidural space and was attached to the flaval ligaments by a dorsomedian connective tissue band. The band was identified in all eight subjects and was found to cause a dorsal fold in the dura mater. An epidural catheter was introduced 2–5 cm into the space by midline puncture in four patients and by the paramedian approach in the other four. The catheter was visualized in two patients only when the paramedian approach was used. None of the midline catheters could be seen in the space. In 2 of the 10 subjects a moderate bleeding impaired the view and made complete examination impossible. Smaller bleeding occurred in three other subjects. The partial laminectomy performed one to two interspaces caudad to the level of endoscopy did not reveal any evidence of epidural bleeding in any subject. The postoperative course of all patients was uneventful.

Key Words: ANESTHESIA—epidural. ANATOMY—epidural space.

A study of the anatomy of the lumbar epidural space in humans using endoscopy in human autopsy subjects was presented in 1986 (1) after presentation of the method of epiduroscopy (2). Until then only brief reports had been published of limited observations of the epidural space in connection with spinaloscopy in patients (3–8). In a study of 48 autopsy subjects (1), a dorsomedian connective tissue band of a variable appearance was demonstrated in each case. The band caused a fixation of the dura mater to the flaval ligaments. In 46 instances, a dorsomedian fold of the dura mater was also exposed. The epidural space was easily established in this material when necessary by injecting small amounts of air and usually remained open. However, conclusions cannot be directly transferred from autopsy studies to the situation of clinical epidural anesthesia. The main differences in the relations of the epidural space between cadavers and living humans include the absence of circulation and the very low or completely absent pressure of the cerebrospinal fluid demonstrated in the study with epiduroscopy (1). These factors may influence the appearance of the epidural space.

With the aim of comparing the anatomic relations of the lumbar epidural space in living humans with those already demonstrated in cadavers, a study was performed with epiduroscopy in 10 patients scheduled for partial laminectomy and excision of a herniated lumbar intervertebral disc. Patients having this type of surgery were selected because during the laminectomy any major complication of epiduroscopy that might occur, e.g., an epidural hemorrhage, could be observed.

Methods

Epiduroscopy was performed in 10 patients aged 36 to 61 years. Four were women. All were classified as ASA physical status 1. To minimize risks of bleeding, the patients were instructed to avoid analgesics containing acetylsalicylic acid 1 week before the opera-

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Address correspondence to: Dr. Blomberg, Department of Anesthesia, Central Hospital, S-601 82 Norrköping, Sweden.

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Table 1. Results of Epiduroscopy in 10 Patients

Pt. no.	Level of herniated disc	Level of endoscopy	Epidural space visualized	Complete examination	Complications	Dorsomedian connective tissue band	Dorsomedian fold of dura mater	Catheter introduced and length in epidural space	Catheter visualized
1	L4–5 sin	L2–3	Yes	No	Moderate bleeding	—	—	—	—
2	L5–S1 sin	L2–3	Yes	Yes	None	Yes	Yes	Midline 2 cm	No
3	L5–S1 sin	L3–4	Yes	Yes	Slight bleeding	Yes	Yes	Midline 3 cm	No
4	L5–S1 dx	L2–3	Yes	Yes	Slight bleeding	Yes	Yes	Midline 5 cm	No
5	L5–S1 dx	L2–3	Yes	Yes	Slight bleeding	Yes	Yes	Midline 5 cm	No
6	L5–S1 dx	L2–3	No	No	Moderate bleeding	—	—	—	—
7	L4–5 sin	L2–3	Yes	Yes	None	Yes	Yes	Paramedian 5 cm	Yes
8	L4–5 dx	L2–3	Yes	Yes	None	Yes	Yes	Paramedian 5 cm	No
9	L4–5 sin	L2–3	Yes	Yes	None	Yes	Yes	Paramedian 5 cm	Yes
10	L5–S1 dx	L2–3	Yes	Yes	None	Yes	Yes	Paramedian 5 cm	No

tion. All had normal coagulation tests and platelet count on admission. Patients with a prominent stenosis of the spinal canal were not included in the study for technical reasons. The patients gave informed consent to participation in the study. Approval was obtained by the Ethical Committee of the Medical Faculty, University of Linköping.

Epiduroscopy was performed before the laminectomy, under general anesthesia, with complete muscle relaxation. The patient was placed in a lateral position with the side of the disc herniation upward. The distance to the epidural space was first determined with the aid of an 18-gauge Tuohy needle in the midline of the interspace L3–4 (in one subject L4–5). A rigid needle arthroscope, the Olympus Selfoscope, with an external diameter of 2.2 mm or 1.7 mm (in one patient), and with the lens directed 90° to the length of the endoscope, was introduced percutaneously in the interspace L2–3 (in one subject L3–4). The epidural space was visually identified. Repeated small injections of air, 3–5 ml at a time, were made through the Tuohy needle to open the epidural space. Examination of the epidural space was complete in 8 of the 10 patients. Reasons for incomplete examination in two patients are stated in Table 1. An epidural catheter (Vygon, polyamide, external diameter 1.0 mm) was introduced one interspace caudad to the level of endoscopy using midline approach in four patients and paramedian approach in the other four. The catheter was advanced 2–5 cm into the epidural space. Photographic documentation of the appearance of the epidural space was attempted using Ektachrome 400 ASA color film or Ilford HP5 400 ASA black and white film.

Results

Detailed results of the study are presented in Table 1. The level of endoscopy was at the interspace L2–3 in all but one patient (No. 3), in whom narrow conditions necessitated the use of the thin endoscope and success was obtained at the level L3–4. A moderate epidural bleeding in two patients interfered with the epiduroscopy. In one of them the epidural space was visualized, but the epiduroscopy was discontinued because of bleeding. In the other, blood obliterated the vision immediately. Complete epiduroscopic examination, including catheter introduction, was thus possible in eight cases.

The epidural space presented as a potential space that opened up only with difficulty and temporarily as small increments of air were injected (Fig. 1). The dura mater was seen to lie close to the dorsal aspect of the epidural space. The extent of view was very limited compared with the views obtained in autopsy subjects. At most the view was about 1.5–2 cm in the caudal direction and even that view was very restricted laterally.

Fat was found in varying amounts in the epidural space. Vessels were encountered on the dura and the flaval ligaments, as well as in the connective tissue. The dorsomedian connective tissue band was demonstrated as well as a dorsal fold of the dura mater in each of the eight patients with a complete examination. The dura mater was closely attached to the dorsal aspect of the epidural space by this connective tissue band (Fig. 2).

The epidural catheter was introduced through a Tuohy needle in the next interspace caudad to the level of endoscopy. In the four cases in which the midline approach was used it was not possible to visualize the catheter in any subject. After removal, one of these catheters was found to be bent in such a fashion that it was evident that it had been advanced laterally. In the other four patients, in whom the paramedian approach was used, the catheter was visualized in two. The presence of the catheter in the other two was evident because of movement of

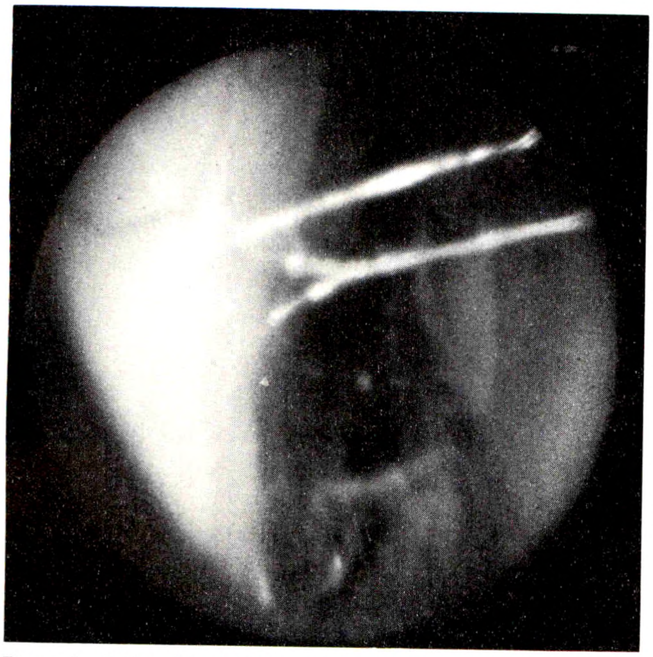

Figure 1. Patient No. 4. Epiduroscopy, caudal view. Dura mater is to the left, flaval ligaments to the right. The epidural space opens up as air is injected revealing some of the strands of connective tissue in the dorsomedian band.

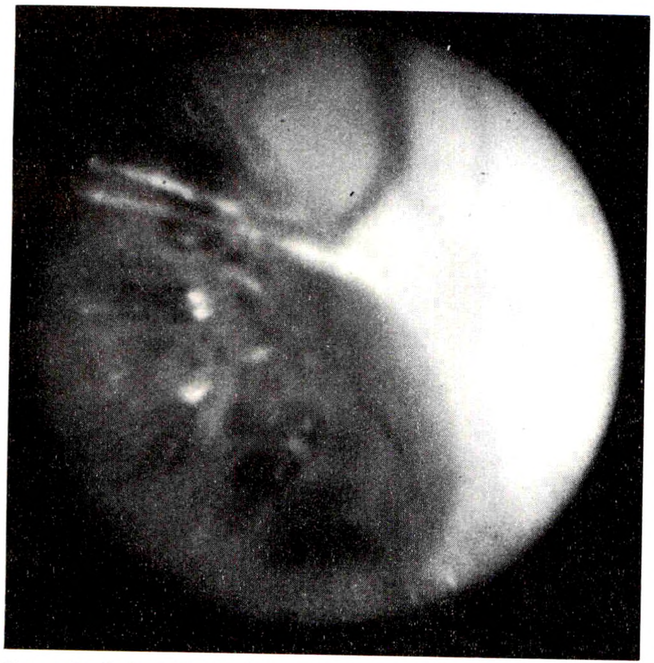

Figure 2. Patient No. 2. Epiduroscopy, caudal view. Dura mater is to the right, flaval ligaments to far left. The dura mater is attached to the dorsal aspect of the epidural space by a fairly heavy dorsomedian connective tissue band.

tissues in the epidural space as the catheter was advanced.

Bleeding was the only complication. In two patients the bleeding, although modest, was sufficient to blur the view and thus make complete epiduroscopic examination impossible. Minor bleeding in three other subjects did not disturb epiduroscopy. No traces of any bleeding were found in these patients during subsequent laminectomy. No perforation of the dura mater was caused by either the trocar and epiduroscope or with the Tuohy needles. The postoperative course was uneventful in each of the patients.

Discussion

This study demonstrated that epiduroscopy can be performed in the patients despite certain difficulties. The extent of view of the epidural space was, however, restricted and estimated to be 1.5–2 cm in the caudal direction and was very limited laterally and in a cranial direction. This contrasts with the findings in autopsy subjects (1) in whom the epidural space readily opened up and usually remained open after injection of small amounts of air.

The information obtained from this investigation indicates that the lumbar epidural space in the living subject is mainly a potential space that rather reluctantly and temporarily opens up as air or fluid is injected. This is in agreement with a similar suggestion by Harrison et al. (9) as a result of their resin injection studies of the lumbar epidural space. Recently, a study of the human epidural space with a combination of computed tomography and epidurography (10) has confirmed the appearance of the dorsomedian connective tissue band, although it was referred to as the plica mediana dorsalis. Together with laterally extending connective tissue bands, the dorsomedian band divided the epidural space into potential compartments.

The contrast between epiduroscopic appearance of the epidural space in patients in this study and the appearance seen in autopsy subjects suggests that the presence of normal circulation and cerebrospinal fluid pressure may be among the factors involved in maintenance of the relations of structures of the epidural space in vivo. The possible influence in this study of positive pressure ventilation and muscle relaxation on factors such as epidural venous pressure and cerebrospinal fluid pressure has not been investigated.

Visualization of the epidural catheter was successful only in two of the four instances in which a paramedian approach was used. The presence of the catheter in the epidural space of the other two patients was suggested by movements of tissues of the epidural space.

The moderate bleeding in patients No. 1 and 6 caused by the introduction of the trocar and epiduroscope made a complete examination impossible. Patient No. 6 admitted postoperatively on questioning that he had taken acetylsalicylic acid up to the day before hospital admission, contrary to the preoperative instructions. This may have been a contributing factor in the bleeding that occurred. The other more minor episodes of bleeding arose during introduction of the catheter into the epidural space and it is notable that in all three instances the midline approach was being used. The findings suggest that minor bleeding in the epidural space may not be uncommon during catheter introduction. The limited number of observations in the present study do not present any conclusive evidence about possible differences in the two methods for epidural approach regarding catheter route and development of bleeding. The observations do, however, give rise to speculation about the proposed advantages of the paramedian approach for lumbar epidural puncture and catheter introduction as demonstrated in a study with epiduroscopy in cadavers (11). Further clinical investigation of these advantages is necessary.

In the study of 48 autopsy subjects (1), a suggestion was made that the extraction of an accidentally cut epidural catheter might be possible with the aid of epiduroscopy. The very restricted conditions of the epidural space in vivo and the tendency for bleeding demonstrated in this study illustrate some of the difficulties that can be expected if such a procedure were to be undertaken. They do not, however, contradict the possibility of a successful endoscopic extraction.

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REVIEW ARTICLE

Clinical Uses of Intravenous Anesthetic and Analgesic Infusions

Paul F. White, PHD, MD

Key Words: Anesthetic Techniques, intravenous.

An increasing interest in intravenous (i.v.) anesthetic techniques has resulted from the availability of more efficacious i.v. drugs, the toxicity of traditional volatile anesthetics (and high cost of newer agents), and concern over anesthetic gas pollution in the operating and recovery rooms. Nevertheless, inhaled anesthetics remain extremely popular because they are generally considered to be more controllable and hence easier to use during surgery. That is, rapid changes in the depth of anesthesia are possible because of the rapid uptake or elimination of inhaled anesthetics from the lungs. The use of inhaled anesthetics is also facilitated by the availability of a convenient delivery system designed to optimize titration of these drugs.

It is possible that i.v. anesthetics (and analgesics) could be made more controllable, and hence more like the volatile anesthetics, if they were administered by a continuous variable-rate infusion rather than by intermittent bolus injection (1). The traditional intermittent bolus administration of i.v. anesthetics (and analgesics) results in rapid increases and decreases in blood concentrations of these drugs. As a consequence, the depth of anesthesia (or analgesia) often oscillates above and below the desired level. However, by more closely titrating the drug, it is possible to minimize the "peaks and valleys" in blood concentrations and thereby, decrease the amount of drug administered, improve anesthetic conditions, and shorten recovery times (Table 1). In addition, the narrower band of blood and brain anesthetic (and analgesic) concentrations provided by continuous infusion techniques might provide greater intraoperative hemodynamic stability and decrease side effects (Table 2). The availability of a monitor that could provide an objective measure of "depth of anesthesia" would further enhance our ability to administer i.v. anesthetics and analgesics.

During the last decade, an increasing number o reports have appeared in the anesthesia literature describing continuous infusion techniques for administering a variety of i.v. anesthetic and analgesic drugs (1–20). In this article, the use of continuous infusion techniques for administering anesthetics and analgesics during and after surgery is reviewed.

Characteristics of an Ideal i.v. Anesthetic and Analgesic

Thiopental, a rapid and short-acting thiobarbiturate was introduced into anesthesia more than fifty years ago by Waters and Lundy. Since that time, thiopenta has proved so useful that it remains the "gold standard" against which more recently introduced i.v drugs are compared. Despite its many desirable properties (e.g., rapid and smooth onset of sedative hypnotic effects, predictable pharmacologic effects rapid and smooth emergence without disturbing side effects), thiopental is by no means the ideal intravenous anesthetic.

The physicochemical and pharmacologic properties which an ideal i.v. anesthetic would possess include: 1) highly soluble in water, nonirritating to tissues, and stable in solution with a long shelf-life; 2) a rapid (one arm-to-brain circulation time) and smooth induction of anesthesia without disturbing excitatory activity; 3) no hypersensitivity reactions; 4) lack of depressant effects on the cardiovascular and respiratory systems; 5) produces decreases in major organ metabolism that exceed decreases in organ perfusion; 6) rapid elimination (short elimination

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Address correspondence and reprint requests to Dr. White, Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110.

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Table 1. Comparison of Total Dosages and Recovery Times when i.v. Drugs are Administered by the Traditional Intermittent Bolus Technique and by a Variable-rate Infusion (1,10)

	Fentanyl		Ketamine		Alfentanil	
	Bolus	Infusion	Bolus	Infusion	Bolus	Infusion
Total dose (μg or mg)	422 ± 19	233 ± 14*	176 ± 11	101 ± 8*	2.5 ± 0.3	1.6 ± 0.1*
Duration of anesthesia (min)	23 ± 1	23 ± 1	22 ± 1	22 ± 1	24 ± 1	23 ± 2
Recovery times						
awakening (min)	5.3 ± 0.6	2.0 ± 0.3*	8.3 ± 1.0	3.3 ± 0.5*	2.5 ± 0.3	1.2 ± 0.1*
discharge (h)	1.4 ± 0.2	1.0 ± 0.1*	1.6 ± 0.2	1.4 ± 0.1	0.8 ± 0.07	0.7 ± 0.05
Postoperative side effects (%)						
nausea	64	56	32	36	52	68
dizziness	40	32	64	41	24	28
fatigue	56	38	82	44*	28	12*
sedation	48	4*	52	8*	16	8*

*Significantly different from bolus injection group, $p < 0.05$.

Table 2. Comparison of a Continuous Opioid Infusion and Intermittent Bolus Injections During "Balanced" Anesthesia for Scoliosis Fusion Surgery (5)

	Morphine		Fentanyl	
	Bolus	Infusion	Bolus	Infusion
Total dose ($\mu g \cdot kg^{-1}$)	1280 ± 206	820 ± 187*	30 ± 9	13 ± 6*
Nitroprusside ($\mu \cdot kg^{-1}$)	30 ± 7	2 ± 1*	0.8 ± 1.2	1.6 ± 2.3
Wake-up test (min)	>5	<5	>5	<5
Narcotic antagonist	Yes	No	Yes	No
Respiratory depression (%)†	43	11*	50	0*

*Significantly differnet from bolus group, $p < 0.05$.
†Required ventilatory support during the early postoperative period.

half-life) and/or biotransformation into inactive, nontoxic metabolites to minimize accumulation with prolonged administration; 7) rapid and smooth emergence without side effects; and 8) analgesic properties at subanesthetic levels.

Although the ideal i.v. anesthetic agent is yet to be developed, a wide spectrum of i.v. drugs can be infused either alone (e.g., ketamine) or in combinations (e.g., propofolalfentanil) to produce general anesthesia. Total intravenous anesthesia typically involves the use of a combination of sedative-hypnotic, opioid analgesic, and neuromuscular relaxant drugs.

Clinical Situations in Which Continuous Administration Techniques are Useful

In recent years, studies have indicated that both sedative-hypnotic and opioid analgesic drugs can be successfully administered by continuous infusion techniques during general anesthesia (Table 3). Early studies demonstrated that opioid infusions could be useful adjuvants to nitrous oxide and muscle relaxants during "balanced" anesthesia (2,3). Other classes of i.v. drugs can also be highly effective when administered by i.v. infusion both during and after surgery.

Table 3. Uses of Continuous Infusion Techniques for Administering Sedative, Hypnotic and Analgesic Drugs

I. Adjunctive (supplemental agents during surgery
  A. Sedative-hypnotic infusions
    1. local or regional anesthesia
    2. brief outpatient procedures
    3. neurological surgery
  B. Opioid analgesic infusions
    1. cardiac surgery
    2. scoliosis fusion surgery
    3. general (intra-abdominal) surgery
  C. Ketamine infusions
    1. one-lung anesthesia
    2. cardiac tamponade
    3. supplement local or regional anesthesia
II. Total intravenous anesthetic techniques
  A. Sedative-hypnotic/opioid/muscle relaxant
  B. Benzodiazepine/ketamine/muscle relaxant
III. Postoperative sedation and/or analgesia
  A. Opioid analgesic infusions
  B. Benzodiazepine infusions
  C. Ketamine infusions

Infusions of sedative-hypnotic drugs (e.g., methohexital, midazolam, propofol) can be used as alternatives to volatile agents or nitrous oxide (18,21). When continuous sedation is required during local or regional anesthesia, infusions of sedative-hypnotic drugs can also be useful alternatives to nitrous oxide or intermittent bolus injections of benzodiazepine (22). Thiopental, methohexital, and etomidate have been used for this purpose, but propofol may offer advantages because recovery is rapid due to its short elimination half-life and a low incidence of postoperative side effects (23,24). With the availability of potent, rapid, and shorter-acting benzodiazepines (e.g., midazolam), it might also be advantageous to administer these sedative-anxiolytic compounds by a continuous, variable-rate infusion (11,16). In addition to their sedative and hypnotic properties, benzodiazepines also possess profound amnestic properties.

Prolonged postoperative sedation and analgesia have been achieved with infusions of midazolam and opioids, respectively (9,11,16). Although prolonged infusions of etomidate can provide effective sedation in the ICU (25,26), its use is not recommended in this situation because of the risk of septic complications secondary to etomidate-induced adrenal suppression. Finally, numerous reports have appeared in the anesthesia literature describing the use of ketamine infusions alone and in combination with other adjunctive anesthetic agents during and after surgery (27,28).

Techniques for Continuous Administration of Intravenous Drugs

Titration of i.v. sedatives and analgesics using incremental bolus doses has been used by anesthesiologists for many years. Continuous infusion is a logical extension of this method of drug titration, thereby minimizing the fluctuations in the blood (and hence brain) concentrations that follow each bolus injection. In order to more rapidly achieve a therapeutic blood level, it is necessary to administer a "loading" dose. To maintain the desired drug concentration, it is then necessary to use a continuous "maintenance" infusion. Although i.v. infusions are generally titrated on an empirical (clinical) basis, a knowledge of basic pharmacokinetic principles may allow the anesthetist to more accurately predict the dosage requirements in a given situation. Pharmacokinetic data can be used to calculate the loading dose (LD) and an initial maintenance infusion rate (MIR) for continuous infusion techniques. Two simple equations can be used to estimate LD and MIR:

$$\mathrm{LD}\ (\mu\mathrm{g}\cdot\mathrm{kg}^{-1}) = \mathrm{Cp}\ (\mu\mathrm{g}\cdot\mathrm{ml}^{-1}) \times \mathrm{Vd}\ (\mathrm{ml}\cdot\mathrm{kg}^{-1})$$

$$\mathrm{MIR}\ (\mu\mathrm{g}\cdot\mathrm{kg}^{-1}\cdot\mathrm{min}^{-1}) = \mathrm{Cp}\ (\mu\mathrm{g}\cdot\mathrm{ml}^{-1}) \times \mathrm{Cl}\ (\mathrm{ml}\cdot\mathrm{kg}^{-1}\mathrm{min}^{-1})$$

where Cp = plasma drug concentration, Vd = volume of distribution, and Cl = clearance of drug.

Because achievement of steady-state drug concentrations with a constant infusion is a slow process (requiring 3–5 drug half-life periods), and LD is necessary. The LD can be administered as either a bolus or as a rapid "priming" infusion (to minimize the acute side effects associated with a bolus injection). Since side effects are more common with rapid fluctuations in drug concentrations, a loading infusion may be preferred to a loading bolus. The required Cp will depend on the desired pharmacologic effect (e.g., analgesia, sedation, hypnosis), the presence of other centrally active drugs (e.g., nitrous oxide, volatile agents, opiates, sedative-hypnotics), the type of operation (e.g., superficial, intra-abdominal), and the individual's sensitivity to the drug (e.g., age, degree of anxiety, drug history).

Data available from the literature regarding Cp, Vd (i.e., central [Vc] and steady-state [Vd_{ss}] volumes of distribution), and Cl values for the commonly infused i.v. anesthetic and analgesic drugs are summarized in Table 4. Obviously, preexisting diseases (e.g., cirrhosis, renal failure, congestive heart failure) can markedly alter many of these kinetic variables. Age is also an important factor to consider when using infusion techniques. In general, children have higher Cl rates, but the elderly often have reduced Cl values. Vd_{ss} values also tend to be larger in the elderly because of an age-related decline in muscle mass and a greater proportion of body fat.

In the LD equation, use of the *smaller* Vc value for the Vd component may underestimate the required LD, whereas use of the *larger* Vd_{ss} value will result in drug levels which transiently exceed those that are desired (Fig. 1). The smaller the LD, the greater the initial MIR needed because the amount of drug infused must equal that which is effectively removed from the brain by both redistribution and elimination processes. With time, redistribution assumes less importance, and the infusion rate required to maintain a given drug level becomes dependent solely on the drug's elimination rate. In this situation, the MIR required to maintain a therapeutic drug concentration would be expected to decrease during the infusion period. Although computer programs are available that allow prediction of concentration-time profiles for i.v. anesthetics and analgesics based on population pharmacokinetics (29,30), their clinical usefulness is unclear given the marked pharmacokinetic (Fig. 2) and pharmacodynamic (Figs. 3, 4) variability that exists among surgical patients. In clinical practice, the anesthesiologist must always titrate the rate of drug administration according to the clinical situ-

Table 4. Range of Plasma Concentrations and Pharmacokinetic Variables Used to Calculate Loading Dose and Initial Maintenance Infusion Rate*

Drug (Trade name)	Cp (μg·ml^{-1})†	Vc (L·kg^{-1})	Vdss (L·kg^{-1})	Cl (ml·kg^{-1}·min^{-1})
thiopental (Pentothal^{R})	5–20	0.4	2.5	3
methohexital (Brevital^{R})	1–4	0.3	2	11
etomidate (Amidate^{R})	0.1–0.5	0.3	4	17
propofol (Diprivan^{R})	1–10	0.3	2	30
morphine sulfate	0.02–0.2	0.3	3	14
meperidine (Demerol^{R})	0.3–2.0	0.7	4	11
fentanyl (Sublimaze^{R})	0.002–0.035	0.6	4	13
sufentanil (Sufenta^{R})	0.0002–0.002	0.1	2.5	11
alfentanil (Alfenta^{R})	0.05–0.5	0.15	0.7	6
ketamine (Ketalar^{R})	0.5–2.5	0.5	3	18
midazolam (Versed^{R})	0.05–1.0	0.4	1.5	7

*Values derived by averaging data available from the anesthesia and pharmacokinetic literature.

†Factors that determine the clinically effective plasma drug concentration include patient's age, drug history, level of anxiety, type of operation, and supplemental agents.

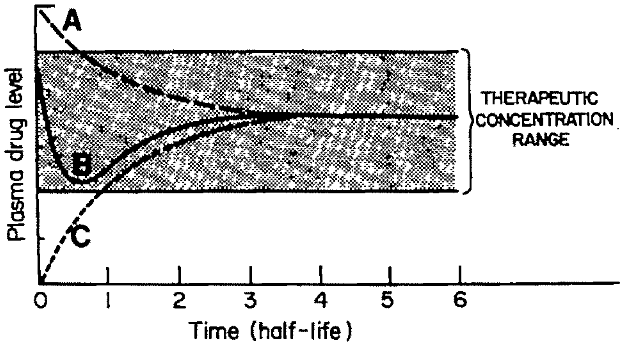

Figure 1. Simulated drug level curves when a constant infusion is administered following a "full" loading dose equal to [Cp] times Vdss (A), a smaller loading dose equal to [Cp] times Vc (B), or in the absence of a loading dose (C).

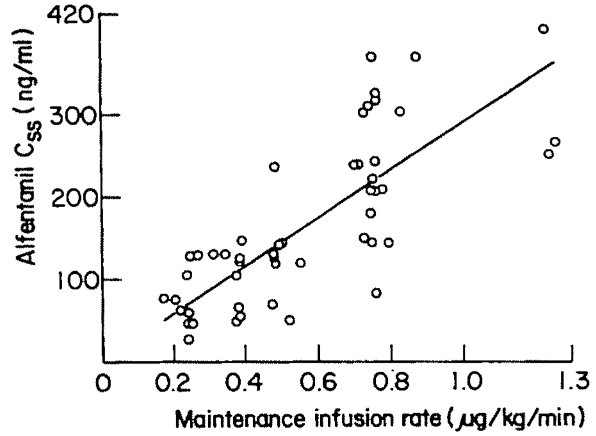

Figure 2. Relationship between maintenance infusion rate (MIR) and resultant steady-state alfentanil concentration (C_{ss}) during nitrous oxide-narcotic-relaxant anesthesia. The infusion rate was maintained at a constant rate for a minimum of 60 min. Correlation coefficient (regression analysis) is 0.95 between MIR and C_{ss} (reproduced with permission from Shafer et al., 1983) (12).

ation (i.e., individual patient's response to a given surgical stimulus).

When i.v. anesthetics and analgesics are used as adjuvants to nitrous oxide (i.e., "balanced" anesthesia) or as sole anesthetics (i.e., total intravenous anesthesia), what clinical signs are most useful in deciding whether to increase or decrease the MIR? The most sensitive clinical signs of depth of anesthesia appear to be changes in muscle tone and ventilatory pattern. However, if the patient has been given muscle relaxants, the anesthesiologist must rely on autonomic hyperactivity (e.g., diaphoresis, lacrimation, tachycardia, hypertension). Although the blood pressure response to surgical stimulation is a useful guide in judging the depth of anesthesia with the volatile anesthetics, it may be a less reliable index when i.v. drugs are used.

In response to a standardized stimulus, patients might be expected to respond with similar increases in peripheral vascular resistance at similar depths of anesthesia. However, the blood pressure response also depends upon the ability of the heart to maintain the cardiac output in the face of an increased afterload. Thus, changes in vascular resistance may be a more reliable indicator of adequacy of anesthesia than alteration in mean arterial pressure. In addition, the heart rate response to surgical stimulation may also be a more useful guide than blood pressure in determining the need for additional anesthetic or analgesic medication. In clinical studies, changes in "stress" hormone levels (e.g., catecholamines, vasopressin, ACTH, growth hormone) are frequently used to assess the adequacy of a given anesthetic technique. Unfortunately, a reliable "depth of anesthesia" monitor is not available. Although the EEG can be useful in quantitating the central effects of anesthetic drugs in the absence of surgical stimulation, its value as a

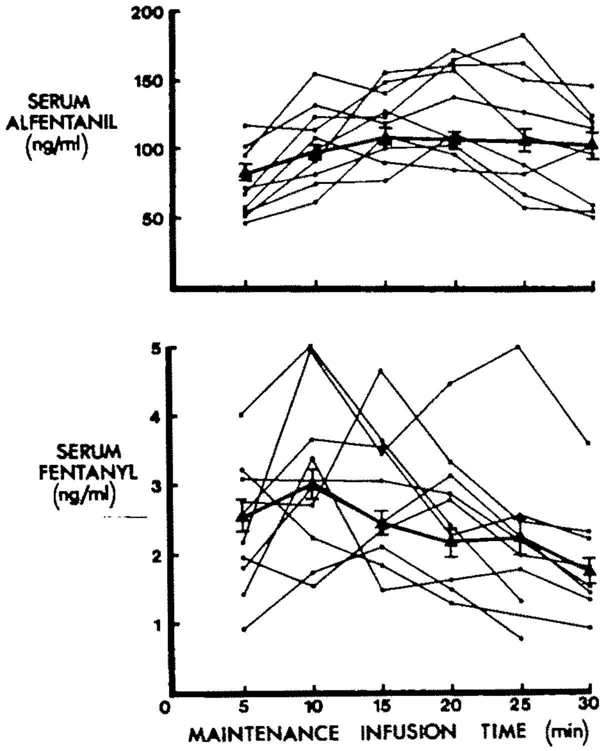

Figure 3. Serum fentanyl (lower panel) and alfentanil (upper panel) concentrations required during brief outpatient gynecologic procedures. Average serum concentrations (solid symbols) are shown as a function of time during maintenance infusion. All patients were undergoing the same operation under identical anesthetic and surgical conditions (reproduced with permission from White et al., 1986) (10).

monitor of depth of anesthesia during surgery is unproven.

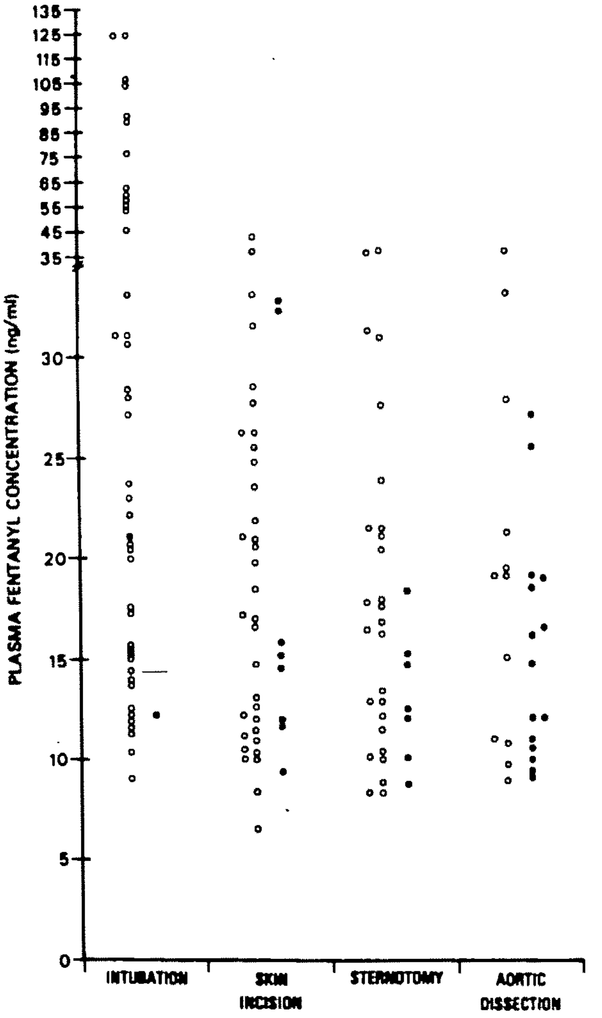

Figure 4. Relationship between plasma fentanyl concentrations and hemodynamic responses to specific stimuli during cardiac surgery. At each event studied, patients either remained normotensive (○) or became hypertensive (●) (reproduced with permission from Wynands et al., 1984) (41).

If a continuous infusion technique is to be used in an optimal manner to suppress clinical responses to surgical stimulation, the drug's MIR should be varied according to individual patient responses, analogous to the fashion in which volatile anesthetics are administered. Attempting to use a constant MIR large enough to suppress responses to the most intense surgical stimulus during an operation could lead to excessive drug accumulation and postoperative side effects (e.g., sedation, respiratory depression). Gradual increases or decreases in blood pressure or heart rate are usually treated by 25–50% increases or decreases, respectively, in the MIR. However, abrupt increases in blood pressure, heart rate, or clinical sign of excessive sympathetic activity (e.g., lacrimation, diaphoresis, flushing) can be treated by giving small bolus doses (equal to 10–25% of the initial LD) and then increasing the MIR by 50–100%. Alternatively, vasodilators (e.g., volatile agents, hydralazine, nitroglycerin, nitroprusside), β-adrenergic blockers (e.g., propranolol, esmolol, labetalol), and alpha$_2$-agonists (e.g., clonidine, medetomidine) can be used to blunt the hemodynamic responses to more stressful surgical stimuli and thereby, decrease anesthetic and analgesic drug requirements.

During the operation, MIR should be gradually decreased until the patient has clinical sign(s) of inadequate anesthesia or analgesia. If the drug is properly titrated during surgery, it will not be necessary to use an antagonist at the end of the operation, and the patient will emerge rapidly following discontinuation of the anesthetic drugs. When naloxone is used to reverse residual opioid effects, the lowest effective dose (0.04–0.08 mg, i.v.) should be used to avoid precipitating a hypertensive response to pain. If an excessive amount of narcotic has been administered, the agonist-antagonist nalbuphine, 0.05–0.15 mg·kg^{-1} i.v., may be capable of antagonizing the residual opioid-induced respiratory depression and

Table 5. Delivery Systems Available for Continuous Administration of Intravenous Drugs

Systems	Advantages	Disadvantages
drip chamber	simplicity low cost	gravity-dependent, lack of precision
flow controller	simplicity	gravity-dependent
syringe pump	accuracy, alarms	initial expense
volumetric pump	accuracy, alarms	initial expense, on-going expense
computerized pump	accuracy, alarms	initial expense

sedation without completely reversing the analgesic effects of the pure opioid agonist. Flumazenil (Ro 15-1788), 5–15 $\mu g \cdot kg^{-1}$, can be used to rapidly and effectively reverse residual benzodiazepine-induced sedation and amnesia. Use of minimally effective doses of flumazenil will avoid precipitating acute stress responses.

A wide variety of delivery systems are available for i.v. infusion techniques (Table 5). Although volumetric or syringe pumps are essential for prolonged infusions, drip chambers (with or without a flow-controller device) are adequate for shorter cases. Drip chambers containing the anesthetic or analgesic can be incorporated or "piggy-backed" into an existing i.v. line. Although volumetric pump systems are widely used for infusing drugs outside the operating room, syringe pumps are easier to use during and after surgery and do not require expensive pump infusion sets. A convenient syringe infusion pump is currently available for administering the opioid analgesic alfentanil. Using an interchangeable face plate, this pump has been adapted for infusing other types of intravenous anesthetics and analgesics (R. Kalaysian, Duke University, personal communication). The concentrations of the drug solutions that are infused can be varied depending on the expected dosage requirement and the delivery system used. If a highly accurate mechanical pump with a fail-safe alarm system is used, infusion of undiluted drug solutions minimizes preparation time. However, when less precise drug delivery systems are employed, more dilute solutions are probably easier and safer to use.

Computer-assisted continuous infusion devices have been developed which utilize pharmacokinetic variables to rapidly obtain and maintain constant drug levels of intravenous anesthetics and analgesics (6,31). To date, it has not been demonstrated that these sophisticated drug infusion systems decrease variability in patient responses to an administered dose of an i.v. anesthetic or analgesic drug. These pharmacokinetically based infusion devices are comparable to manual intermittent (bolus) injection methods for maintaining hemodynamic stability during general anesthesia (31,32). The future of computer-controlled infusion systems for administering i.v. anesthetics and analgesics depends on the reliability and cost-effectiveness of the automated infusion devices. Furthermore, the clinical usefulness of computer-driven drug administration systems needs to be established.

Sedative-Hypnotic Infusions for Sedation and as Adjuvants to Nitrous Oxide for Outpatient Anesthesia

Patients undergoing surgery with local or regional anesthesia frequently desire sedation to minimize anxiety and to prevent recall of intraoperative events. Although intermittent bolus injections of sedative-hypnotic drugs (e.g., diazepam, 2.5–5 mg, midazolam, 1.25–2.5 mg, thiopental 25–75 mg) are commonly administered, the effect is often short-lived because these drugs are rapidly redistributed from vessel-rich tissues to lean muscle and fat. To achieve a stable level of sedation, infusions of thiopental (1–5 $mg \cdot min^{-1}$) or methohexital (0.5–2.5 $mg \cdot min^{-1}$) have been used. Prolonged infusions of methohexital should be associated with a more rapid recovery than thiopental because the clearance rate of methohexital is three-to-four times more rapid, resulting in a shorter elimination half-life (3–5 h *versus* 10–12 h). The use of propofol for infusion may offer advantages over use of barbiturates for prolonged sedation because its shorter elimination half-life (1–3 h) would be expected to contribute to an even more rapid recovery.

Recently, we compared the sedative, amnestic, and recovery characteristics of methohexital, etomidate and midazolam when infused during regional anesthesia (22). Although midazolam provided more effective intraoperative sedation and amnesia, recovery of psychomotor function was slower with midazolam than with methohexital or etomidate. Midazolam has a relatively short elimination half-life (2–4 h), but the duration of action of this benzodiazepine can be highly variable. Nevertheless, midazolam infusions are useful for sedating critically ill patients requiring tracheal intubation and ventilatory support (11,16). Compared to midazolam, propofol infusion may allow for more rapid weaning of critically ill patients from artificial ventilation because of its ease of titration and shorter duration of action (17,33).

Sedative-hypnotic infusions can also be useful adjuvants to nitrous oxide during brief outpatient procedures as alternatives to the volatile anesthetics. In outpatients receiving fentanyl, 50–100 μg, i.v. (or sufentanil 5–15 μg i.v.), an induction dose of thiopental, 2–4 mg·kg^{-1} i.v., followed by a maintenance infusion of thiopental, 10–20 mg·min^{-1}, can be used to supplement nitrous oxide, 70% in oxygen. However, use of a maintenance infusion of methohexital, 4–8 mg·min^{-1}, with nitrous oxide instead of thiopental may be associated with shorter recovery times and less postoperative sedation and drowsiness (34). When methohexital infusions were used during nitrous oxide anesthesia in patients premedicated with morphine (0.15 mg·kg^{-1}), the minimally effective infusion rate was 75 μg·kg^{-1}·min^{-1} (35).

Controversy surrounds the use of etomidate in anesthesia (26). In outpatients premedicated with fentanyl, 1–2 μg·kg^{-1}, an induction dose of etomidate, 0.2–0.4 mg·kg^{-1}, followed by a maintenance infusion of etomidate, 1–2 mg·min^{-1}, with nitrous oxide 70% in oxygen was associated with intraoperative cardiorespiratory stability (34). Although recovery was rapid, there was a high incidence of postoperative nausea and vomiting. Recent reports have described the use of an etomidate infusion as part of a total i.v. anesthetic technique involving opioid analgesics and muscle relaxants. Following an induction dose, etomidate has been infused at a rate of 10–20 μg·kg^{-1}·min^{-1} to maintain adequate hypnosis (36,37). For example, when used as an alternative to inhaled agents during one-lung anesthesia, a priming infusion of etomidate, 1 mg·kg^{-1}, followed by a MIR of 10 μg·kg^{-1}·min^{-1} results in a satisfactory intraoperative and postoperative course. The anesthetist using etomidate needs to be aware that even a single induction dose (0.2–0.4 mg·kg^{-1}, i.v.) produces transient postoperative suppression of adrenocortical function (26). Although the clinical significance of this side effect is unknown, the use of etomidate should probably be restricted to situations in which it offers a significant advantage over the other available i.v. agents.

The rapid and short-acting sedative-hypnotic propofol is highly effective when administered by continuous infusion during surgery. When used as an adjuvant to nitrous oxide, propofol (4–12 mg·min^{-1}) compared favorably with methohexital (3–11 mg·min^{-1}) for outpatient anesthesia (13). The low incidence of postoperative nausea and vomiting and rapid return to a "clear-headed" state contributed to shorter ambulation and discharge times (compared to methohexital). The hemodynamic responses during anesthesia with propofol, 50–100 μg·kg^{-1}·min^{-1}, and nitrous oxide were similar to other intravenous anesthetics (15,38). In a recent study, propofol infusion (2.5–15 mg·min^{-1}) compared favorably to isoflurane when used as an adjuvant to nitrous oxide for outpatient anesthesia (39). Subhypnotic infusions of propofol, 1–10 mg·min^{-1}, also provide effective sedation during regional anesthesia (23,24). Compared to methohexital, propofol produced a smoother intraoperative and postoperative course with a rapid, uneventful recovery. Analogous to our findings with a midazolam infusion (16), MacKenzie and Grant reported that propofol infusions decreased the requirement for opioid analgesics when used for sedation of agitated, ventilator-dependent patients (17).

Opiate Infusions Alone and in Combination With Nitrous Oxide and Muscle Relaxants for Surgical Anesthesia

The common practice of administering a large dose of fentanyl (50–150 μg·kg^{-1}) at the beginning of cardiac surgery represent an inefficient use of this potent analgesic drug. The fentanyl concentrations, initially excessive, rapidly decline to subtherapeutic levels as a result of the rapid and extensive redistribution of fentanyl. If fentanyl is used as the primary anesthetic during cardiac surgery, it has been suggested that levels in excess of 20 ng·ml^{-1} may be needed to maintain hemodynamic stability (40). A LD of 25–75 μg·kg^{-1} followed by an MIR of 0.3–0.6 μg·kg^{-1}·min^{-1} would be expected to achieve a steady-state fentanyl blood level $\geq$20 ng·ml^{-1}. Other investigators, however, have been unable to accurately define a minimum effective plasma fentanyl concentration because of the marked pharmacokinetic and pharmacodynamic variability in different patients (Fig. 4) (41,42).

Numerous reports have described the use of opioid infusions as part of a balanced technique with nitrous oxide and muscle relaxants. The duration of postoperative analgesia has been reported as being longer and the degree of respiratory depression less with the intravenous infusion of fentanyl than with conventional incremental bolus injections (5). In the early clinical studies, fentanyl was administered both by bolus injection followed by a constant rate infusion (1,40), and by rapid infusion followed by a slower continuous infusion (2,38). For example, in patients undergoing intra-abdominal surgery, a LD of 10 μg·kg^{-1} fentanyl followed by a maintenance infusion of 2 μg·min^{-1} was required to maintain hemo-

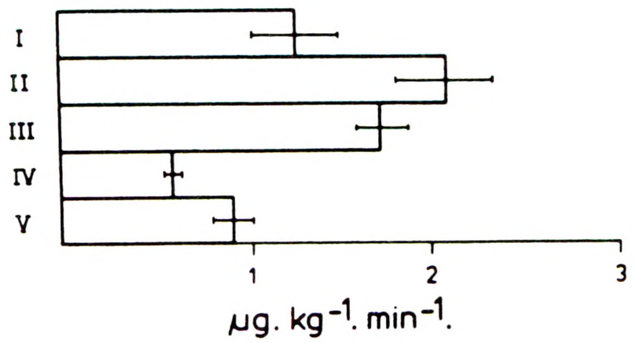

Figure 5. Mean alfentanil dosage requirements ($\mu g \cdot kg^{-1} \cdot min^{-1}$) during lower abdominal surgery: (I) after induction of anesthesia but before skin incision; (II) after skin incision and before placement of abdominal retractors; (III) during intraabdominal manipulation; (IV) during microscopic surgery on the Fallopian tube; (V) after removal of the abdominal retractor before stopping the alfentanil infusion (reproduced with permission from Ausems et al., 1983) (7).

dynamic stability and resulted in steady-state fentanyl levels of 4–8 $ng \cdot ml^{-1}$ (2). In patients undergoing superficial operations, fentanyl 5 $\mu g \cdot kg^{-1}$ followed by a constant infusion of 3 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ resulted in adequate (analgesic) plasma fentanyl concentrations of 3–5 $ng \cdot ml^{-1}$ when used to supplement nitrous oxide (43). More recent studies have evaluated the use of a variable-rate fentanyl infusion in an effort to improve the titration of opioid analgesics (1,5). For outpatients undergoing minor surgical procedures, fentanyl levels of 2–3 $ng \cdot ml^{-1}$ usually provide optimal analgesia in the presence of 70% nitrous oxide (Fig. 3).

Compared to fentanyl (3–12 $\mu g \cdot min^{-1}$), equianalgesic infusions of the short-acting opioid analgesic alfentanil (30–90 $\mu g \cdot min^{-1}$) appear to be associated with less postoperative respiratory depression and residual psychomotor impairment (10). Ausems and colleagues used logistic regression analysis to determine plasma alfentanil concentration-effect curves for different surgical stimuli (14). They concluded that different perioperative stimuli required different alfentanil concentrations to suppress undesirable responses. Because of pharmacokinetic and dynamic variability, the alfentanil infusion rate (Fig. 5) must be varied according to individual patient responses and the magnitude of the surgical stimulus in order to produce satisfactory intraoperative conditions and to provide for a rapid recovery of consciousness and spontaneous ventilation. For superficial surgical procedures, an alfentanil LD of 20–50 $\mu g \cdot kg^{-1}$ followed by a variable MIR of 0.5–1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is generally adequate with nitrous oxide and a muscle relaxant (12). However, more stressful intraabdominal operations may require MIR as high as 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The use of minimally effective infusion rates obviate the need for narcotic antagonists at the end of the operation and decrease the possibility of postoperative respiratory complications and other untoward side effects.

Continuous opioid infusions are becoming increasingly popular during nitrous-narcotic-relaxant anesthesia for spinal fusion surgery (Table 2). As adjuvants to nitrous oxide, the average MIR for morphine and fentanyl range from 2 to 5$\mu g \cdot kg^{-1} \cdot min^{-1}$ and 0.01 to 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively (5). With these MIR rates, wake-up tests are smoother and more repeatable without requiring narcotic antagonists than when opioids are used with incremental bolus injections. A more recent report suggests that a combination of thiopental-alfentanil-vecuronium-N_2O is also highly effective for "wake up" testing during scoliosis surgery (44).

Ketamine Infusions Alone and in Combination With Nitrous Oxide and Muscle Relaxants for Surgical Anesthesia

When ketamine is administered alone, side effects often become problems, including cardiovascular stimulation, postoperative dreaming and confusion (28). Premedication with a benzodiazepine is recommended to decrease ketamine-induced side effects. If ketamine is used as the primary anesthetic for cardiovascular, thoracic or intrabdominal surgery, concomitant administration of midazolam, 0.1–0.2 $mg \cdot kg^{-1}$ i.v., is also highly effective in preventing hypertension, tachycardia, and emergence reactions. After a ketamine LD of 0.5–1.0 $mg \cdot kg^{-1}$, i.v., a MIR of 25–75 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is required to assure unconsciousness and maintenance of hemodynamic stability. In the presence of nitrous oxide 60–70% and a muscle relaxant, an MIR of 10–30 $\mu g \cdot kg^{-1} \cdot min^{-1}$ generally produces adequate anesthetic conditions.

When a ketamine infusion is used to supplement nitrous oxide for maintenance of anesthesia in outpatients undergoing brief surgical procedures, an infusion rate of 2–6 $mg \cdot min^{-1}$ is required (8). Although this anesthetic technique produces excellent intraoperative conditions, recovery is more prolonged than when sedative-hypnotic or opioid infusions are used. Ketamine infusions, 1–2 $mg \cdot min^{-1}$, have also been used for providing sedation and analgesia for ventilator-dependent patients (45). Unfortunately, this technique is frequently unable to provide adequate postoperative analgesia without also producing disturbing psychomimetic reactions (46). Nevertheless, the use of a low-dose ketamine infusion, 0.25–1.0

$mg \cdot min^{-1}$, to supplement benzodiazepine sedation is useful for brief diagnostic and therapeutic procedures outside the operating room (e.g., radiation therapy, emergency room).

Opioid Infusions for Postoperative Analgesia and Sedation

Despite the availability of highly efficacious drugs, patients are frequently undertreated with analgesics after surgery. In no other area of medicine has such an extravagant concern for side effects so drastically limited effective treatment. Analgesics are most effectively used when they are administered by techniques that allow continuous titration to maintain blood and brain concentrations that meet the unique and changing needs of the individual patient. Several studies have evaluated the use of continuous opioid infusion techniques for managing postoperative discomfort (47–51). When a meperidine infusion was used for providing postoperative analgesia after intra-abdominal operations, a LD of 1–2 $mg \cdot kg^{-1}$ (over 30–60 min) followed by a maintenance infusion equal to 0.2–0.8 $mg \cdot min^{-1}$ was required to maintain an effective "analgesic" meperidine level. In morbidly obese patients, a meperidine priming infusion of 1–1.5 $mg \cdot min^{-1}$ (over 30–60 min) followed by a maintenance infusion of 0.3–0.7 $mg \cdot min^{-1}$ was found to provide excellent analgesia without producing respiratory depression during the early postoperative period.

Using an "on-demand" (or patient-controlled) postoperative analgesia device that allowed continuous infusion of a dilute fentanyl or alfentanil solution and small supplemental bolus injections whenever the patient needed additional pain relief, fentanyl and alfentanil requirements averaged 0.5–1.0 and 5–10 $\mu g \cdot min^{-1}$, respectively (49). Although these infusion rates provide useful guidelines, the required opioid (analgesic) dose is highly variable. Both pharmacodynamic variability (e.g., brain sensitivity) and pharmacokinetic differences (e.g., clearance rate) are important in explaining the varying analgesic requirements reported in the literature. Infusion must be carefully titrated to meet the specific analgesic needs of the individual patient.

Patients requiring ventilatory assistance during the early postoperative period often benefit from the analgesic and sedative effects of opioid infusions. Fentanyl and sufentanil infusions are particularly useful in critically ill patients with cardiovascular instability (e.g., after cardiac surgery). Use of prolonged opiate infusions requires careful titration because of the inherent pharmacodynamic variability and the rapid development of tolerance (9). In a double-blind study designed to evaluate if continuous i.v. infusions of opiate analgesics provided more effective postoperative pain relief than conventional intramuscular injections (52), morphine infusions required as much supplemental morphine as did saline (control) infusions to achieve comparable analgesia scores. The authors of this study concluded that a continuous infusion of morphine may be inferior to intermittent bolus injections for postoperative pain relief because the 24 h opioid infusion appeared to facilitate the development of tolerance. Further investigations are clearly needed to define the role of opiate infusions in the management of acute postoperative pain.

Summary

Renewed interest in i.v. anesthetic techniques has resulted from the availability of more rapid and shorter-acting i.v. drugs. With recent advances in the area of infusion pump technology, it has become easier to administer i.v. anesthetics and analgesics by continuous infusion techniques. The newer sedative-hypnotic (midazolam, propofol) and analgesic (sufentanil, alfentanil) drugs are better suited pharmacologically to continuous administration techniques than the traditional i.v. agents because they can be more accurately titrated to meet the unique and changing anesthetic needs of the individual patient.

With the newer sedative and analgesic drugs, it is now possible to administer i.v. anesthetics in a titrated manner analogous to that which is possible when volatile anesthetics are used. In this way, the drug infusion rate is varied depending on the patient's responses to noxious surgical stimuli. In titrating i.v. drug infusions, consideration must also be given to the age of the patient, pre-existing disease states, potential drug interactions, and proximity to the end of the operative procedure. The availability of rapid and short-acting i.v. drugs like alfentanil and propofol, as well as intermediate-acting muscle relaxants (53,54), makes it possible to employ total intravenous anesthetic techniques during general surgery (18,21,57–59).

Many non-sedative and non-analgesic i.v. drugs are being investigated in anesthesia for use by continuous infusion techniques, e.g., muscle relaxant (53,54), and local anesthetics (55,56). Several recent studies have demonstrated the efficacy of continuous infusions of local anesthetics for obstetrical analgesia (55,56). The use of continuous local anesthetic infusions makes it possible to achieve improved analgesia (i.e., a more constant degree of analgesia) with lower doses. Improved delivery systems for administering i.v. drugs will make it easier to use continuous infusion techniques in the future.

With continued progress in the development of infusion devices and i.v. drugs designed for continuous administration, the use of intravenous anesthetic techniques will become more widespread. In the near future, infusion pumps will likely become standard equipment on all anesthesia machines and anesthesiologists should find these techniques easier to use in their clinical practices (60).

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Clinical Reports

Anesthesia Unmasking Benign Wolff-Parkinson-White Syndrome

David Lubarsky, MD, Brian Kaufman, MD, and Herman Turndorf, MD

Key Words: HEART, ARRHYTHMIAS: Wolff-Parkinson-White syndrome.

The anesthetic management of patients with symptomatic Wolf-Parkinson-White syndrome (WPW) undergoing surgical bypass tract ablation has been reviewed (1,2). Rarely, the diagnosis of asymptomatic WPW is made perioperatively. (3) We report two cases of WPW syndrome that were diagnosed perioperatively and that demonstrate how anesthesia may affect patients with intermittent ventricular pre-excitation. Current recommendations for management of intraoperative EKG changes associated with asymptomatic, intermittent Wolff-Parkinson-White (WPW) syndrome are discussed.

Case 1:

A 73-year-old white male with benign prostatic hypertrophy was admitted for transurethral resection of the prostate. Past medical history was negative for cardiac disease or palpitations. There was a 15-year history of peptic ulcer disease treated with antacids and a 1-year history of diet controlled hypertension. Preoperative EKG showed a normal QRS complex, left axis deviation and non-specific ST-T wave changes, as did an EKG obtained one year prior to admission (Fig. 1). Preoperative blood pressure was 110/70 mm Hg, serum sodium was 143 mmol/L, and hematocrit was 43%. Meperidine 75 mg, pentobarbital 100 mg and cefazolin 1 gm were given intramuscularly on call. Spinal anesthesia to a T10 sensory level was accomplished with 9 mg tetracaine in dextrose 10% in water. Intraoperative medications included 5 mg diazepam intravenously, as well as ephedrine and phenylephrine to treat mild intraoperative hypotension (systolic 85-90). Estimated blood loss was one unit and the patient received 600 ml lactated Ringer's solution. The resident anesthesiologist did not notice any EKG changes in the operating room. In the recovery room, the patient arrived with a T6 sensory level, awake and nauseated with a blood pressure (BP) of 100/60 mm Hg and a new wide complex sinus rhythm at 75 beats per minute. A 12 lead EKG demonstrated Type A WPW syndrome (see definition of WPW below) (Fig. 2). At this time arterial blood gas tensions were within normal limits, serum sodium was 122 mmol/L, hematocrit was 35% and rectal temperature was 34.5°C. Furosemide and warmed normal saline were administered. About one hour later, the EKG reverted to its preoperative configuration. At this time serum sodium was 132 mmol/L, rectal temperature was 36°C and there was no nausea or vomiting. The patient was returned to the surgical ward without any further treatment and his subsequent hospital course was uneventful.

Case 2:

A 50-kg, 14-year old boy presented for circumcision. There was no history of palpitations or syncope. Past medical history was negative. Physical examination was significant for a II/VI systolic ejection murmur. Upon arrival in the operative room an intravenous catheter was inserted and 5 mg diazepam was given intravenously. Anesthesia consisted of isoflurane and nitrous oxide with oxygen. After an uneventful operative course, the patient awakened with marked disorientation and combativeness. The patient had some gagging without emesis. BP was 100/60 mm Hg; HR was 90-100 beats/minute. After 10 minutes without improvement, 1 mg of physostigmine was admin-

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Address correspondence to Dr. Lubarsky, Department of Anesthesia, PO Box 3094, Duke University Medical Center, Durham, NC 27710.

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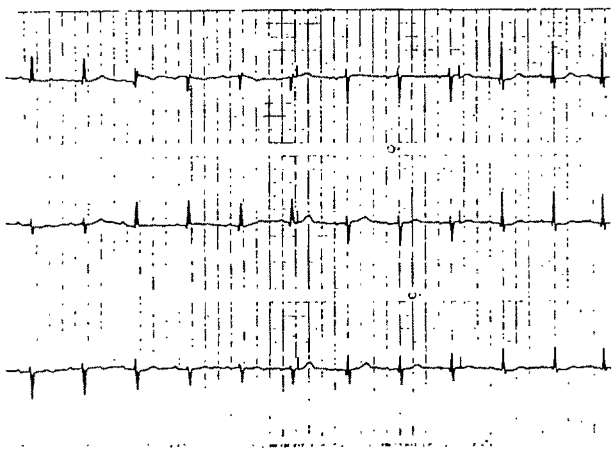

Figure 1. Case 1: Preoperative EKG with narrow QRS complex, sinus rhythm and non-specific ST-T wave changes.

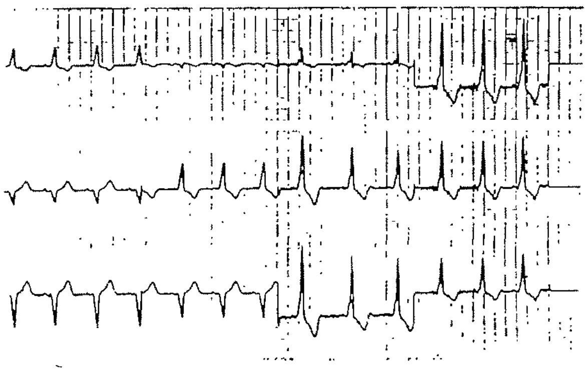

Figure 2. Case 1: Postoperative EKG with type A WPW (right bundle branch block pattern).

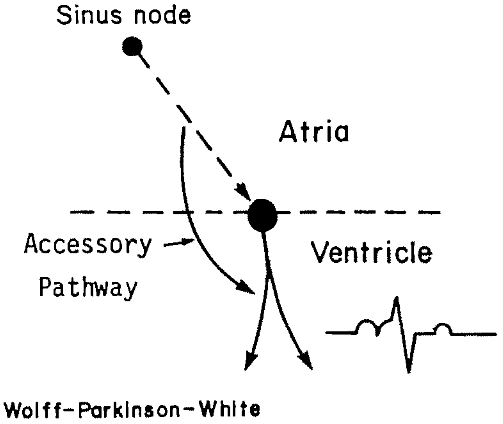

Figure 3. Sinus node impulse traversing either the AV node or bypassing the AV node via the accessory pathway.

istered. Two minutes later a wide-complex sinus rhythm at 80 beats per minute developed with no change in BP. The delirium lessened and the patient was transferred to the recovery room. A 12 lead EKG demonstrated Type A WPW syndrome. The monitor strip showed a narrow QRS with intermittent loss of the delta wave alternating with a right bundle branch block pattern. An echocardiogram revealed no associated cardiac abnormalities. No treatment was given. The patient was returned to the pediatric ward and since then he has done well without any medication.

Discussion

Wolff-Parkinson-White syndrome is the most common of several pre-excitation syndromes. It occurs in 1-3/1000 population. The atrial depolarization usually spreads simultaneously down the A-V node and an anomalous atrio-ventricular connection composed of ventricular muscle-like cells (4). The classic delta wave, widened QRS, and shortened P-R interval represent the atrial impulse prematurely depolorizing some ventricular muscle via the anomalous pathway while the same impulse is also traversing the specialized A-V conduction system (Fig. 3). Two major patterns, Type A and Type B, have been described. When aberrant conduction occurs down a left-sided accessory pathway, a right bundle branch block pattern will be seen on EKG (Type A). With a right-sided accessory pathway, a left bundle branch block pattern will be seen (Type B). Recent electrophysiologic studies have subdivided these pathways anatomically and a complete discussion may be found elsewhere (4,5).

The A-V node utilizes a calcium dependent slow-inward current, while the accessory pathway utilizes a sodium dependent fast-inward current for electrical impulse transmission. The two competing routes of atrioventricular conduction have, therefore, different speeds of depolarization, conduction velocities and effective refractory periods (ERP). The accessory pathway and A-V conduction system may thus be differentially affected by drugs, changes in the electro-physiologic milieu, and/or changes in autonomic tone. Accordingly, conduction through the accessory pathway may occur only intermittently when a permissive environment is present.

The above differences in accessory pathway and A-V node conduction can also predispose to the development of a circus rhythm (an arrhythmia with a circular motion). This arrhythmia involves primarily antegrade A-V conduction (with antegrade unidirectional accessory pathway blockade) with retrograde conduction through the accessory pathway for re-entry into the atrium (Fig. 4). This circular loop gives an EKG tracing with a regular rhythm, a narrow QRS complex, and a tachyarrhythmia at a rate of 120–130 beats per minute (6) that can result in cardiac decompensation.

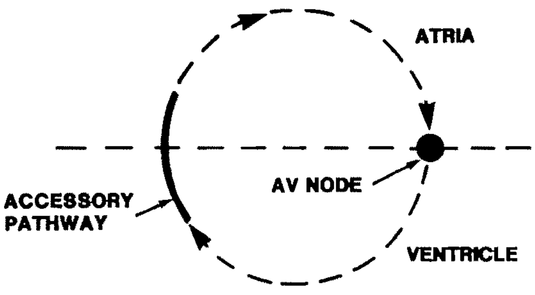

Figure 4. Cirus rhythm: Impulse travels from atria to ventricle via A-V node and then from ventricle back to atria via an accessory pathway.

The second mechanism of arrhythmogenesis involves atrial fibrillation, atrial flutter, or a paroxysmal supraventricular tachycardia conducted antegrade over the accessory pathway at a rapid rate, leading to a rapid ventricular response. This appears on the EKG as a regular or irregular ventricular tachycardia that may degenerate to ventricular fibrillation. Unlike the A-V node, conduction through the accessory pathway is not inhibited at high rates and may conduct each atrial impulse to the ventricle. The A-V node has a built-in safety mechanism which, during atrial flutter or atrial fibrillation, will only allow a portion of the atrial impulses to be transmitted to the ventricle.

In our first case, if the low serum sodium level had any effect, it theoretically should have slowed the conduction velocity of the accessory pathway most, since depolarization of ventricular muscle-like cells in the accessory pathway is primarily sodium dependent. In contrast, in A-V nodal cells slow-inward current is primarily calcium dependent (although, 1/3 of slow-inward current is sodium dependent) (8). However, an increase in vagal tone secondary to hypothermia, nausea, and perhaps, minor sympathetic blockade from the T6 spinal level (9), could have decreased the A-V nodal conduction velocity enough to allow previously obscured conduction via the left-sided accessory pathway to become evident (4). The second case was similar in that physostigmine and gagging probably increased vagal tone and decreased A-V nodal conduction enough to allow initial ventricular depolarization to occur over the left-sided accessory pathway. These two cases demonstrate a low-risk, non-tachycardic, intermittent WPW pattern that does not require therapy. In the only previous case report dealing with the intermittent appearance of WPW syndrome peri-operatively, the patient was treated with lidocaine and observed in an ICU overnight. In the absence of a history of palpitations or syncope, intermittent WPW syndrome is associated with a prolonged ERP of the accessory pathway. This predicts a benign course in the case of rapid atrial rates (4,7). Therefore, pharmacologic treatment and/or telemetry are probably not indicated in this type of patient.

It is important, given the prevalence of WPW syndrome, to differentiate between the benign variant exemplified by our two cases and WPW syndrome in the symptomatic patient who is at risk for hemodynamically significant arrhythmias. If perioperative events unmask WPW syndrome but a detailed history reveals no symptoms, further treatment and studies are probably not warranted.

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General Anesthesia and Fibrodysplasia Ossificans Progressiva

Todd E. Lininger, MD, Eli M. Brown, MD, and Morris Brown, MD

Key Words: COMPLICATIONS—fibrodysplasia ossificans progressiva

Fibrodysplasia ossificans progressiva (FOP), also known as myositis ossificans progressiva, is a rare, inherited disorder with progressive ossification of the connective tissue of muscles and ligaments in association with characteristic skeletal abnormalities (1). The disease is characterized by a progressively debilitating course involving the respiratory system, the musculoskeletal system and the spinal column. Its systemic manifestations create a challenging situation for anesthetic, medical and surgical management. We were unable to find any previous description in the literature of general anesthesia with tracheal intubation and the use of muscle relaxants having been administered to a patient with FOP.

Case Report

A 32-year-old woman with FOP entered the hospital with pelvic pain and an abdominal mass. Ultrasonography revealed a large pelvic mass consistent with a solid tumor, and the patient was scheduled for exploratory laparotomy.

Past medical history was significant only for FOP diagnosed at age 10. She had no previous operations and was receiving no medications. Family history was unremarkable. Review of symptoms revealed primary amenorrhea, inability to walk without assistance, and restriction to liquid diet because of inability to open her mouth.

Physical examination revealed a pleasant, well-nourished, intelligent female in no acute distress. She was supine with a pillow supporting her head and lower extremities. Her neck was fixed in flexion with the jaw fixed at the temporo-mandibular joint. There was minimal range of motion of the lower extremities bilaterally and lateral deviation of the great toes. Stone-hard lesions were present on palpation of most muscle groups. The remainder of the physical examination was unremarkable. Full pulmonary function tests were not performed and the patient refused bedside spirometry.

In the preoperative holding area, the patient was given 0.2 mg glycopyrrolate and 2 mg midazolam intravenously, and 15 ml of 4% lidocaine was nebulized by aerosol mask. On arrival in the operating suite an automatic blood pressure cuff, a pulse oximeter sensor and EKG electrodes were applied. Oxygen saturation by oximetry while breathing room air was 94%. The patient was given 2 mg midazolam, 10 mg ketamine and 25 μg fentanyl intravenously, and the nares were sprayed with 10% topical lidocaine and 0.5% neosynephrine.

Intubation of the trachea was attempted with a 7.0 mm endotracheal tube using a fiberoptic bronchoscope. Although the bronchoscope could be passed into the trachea, the endotracheal tube could not be advanced. A "blind nasal" intubation of the trachea was accomplished using a 6.0-mm endotracheal tube. Mass spectrometric monitoring of expired and inspired gases was instituted and general anesthesia induced using spontaneous ventilation with oxygen/isoflurane. Using a Puritan-Bennett neuromuscular transmission monitor for train-of-four stimulation, the patient was given one mg doses of vecuronium at two-minute intervals to a total of 3 mg (.051 mgm/kg). Two minutes following the third dose, the T1/T4 was .33 and T1 was 36% of baseline levels. Four minutes later (12 minutes after the first dose), T4 was abolished and T1 was 15% of baseline. Intermittent doses (1 mg or .017 mg/kg) of vecuronium were given to maintain adequate muscle relaxation based on train-of-four monitoring. Anesthesia was maintained with isoflurane in oxygen. Surgery consisted of a supracervical hysterectomy with bilateral salpingo-oophorectomy. The intraoperative course was unremarkable. The neuromuscular blockade was easily reversed and the trachea extubated in the operating

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Address correspondence to Dr. Eli Brown, Department of Anesthesiology, Sinai Hospital of Detroit, 6767 West Outer Dr., Detroit, MI 48235.

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room. Postoperatively, close attention was given to the patient's hydration, and she was treated with chest physiotherapy and incentive spirometry. She had an uneventful postoperative course except for a brief period of confusion which resolved spontaneously.

Discussion

FOP was first described by Guy Patin in 1692. Since then, less than 600 cases have been reported in the world literature (2). FOP is an autosomal dominant trait. The clinical picture of FOP as described by numerous authors is remarkably consistent (1,3,4). Initially, the head, neck, spine or shoulders are involved, and these areas tend to be most severely affected as the disease progresses. In the majority of cases, the disease presents by age four (5). All patients have markedly decreased range of motion of the shoulders and spine and are confined to a wheelchair by age 30 (4). In the majority of cases, the disease also involves the muscles of mastication which may progress to complete inability to open the mouth (4) as in this patient. The disease does not appear to involve the diaphragm, esophagus, sphincters, larynx, extraocular muscles, abdominal wall, face, tongue or intestines. Contrary to early reports (4), patients with FOP may be fertile and capable of maintaining a pregnancy (6). Connor et al found that 29% of the patients had abnormal electrocardiograms. The abnormalities included right bundle branch block, T-wave inversion in inferior leads, left axis deviation with ST segment changes and supraventricular tachycardia (7).

The diaphragm is not affected, but ankylosis of the costovertebral joints with chest wall fixation may result in severe pulmonary complications. The most common cause of death, in fact, is pneumonia (3).

The diagnosis of FOP depends on clinical and radiographic demonstration of characteristic skeletal and extraskeletal malformations. Plain radiographs tend to be relatively insensitive to the extent of underlying changes. In early and equivocal cases, CT scan is useful in making the diagnosis (8). It is important to diagnose the disorder at the earliest age possible so that patients are not subjected to events that may precipitate calcification such as multiple biopsies, minor trauma, intramuscular injections and carelessly placed intravenous catheters (4,5).

The term *myositis* is somewhat misleading since connective tissue and not muscle tissue is primarily involved (9). Indeed, skeletal muscle is essentially normal (3). Currently, it appears that there is no specific treatment. Steroids; anti-inflammatory agents; artificial induction of rickets have no significant effect (1,3). Patients benefit, however, from analgesia for pain, antibiotics for recurrent infections, mechanical aids to help them cope with their disability, and genetic counseling.

When general anesthesia is required, it is essential that the airway be secured through intubation while the patient is conscious. In this patient, tracheostomy was technically impossible because of the fixed, flexed position of the head and neck. Even if technically feasible, tracheostomy should be avoided because subsequent ossification at the site of incision could result in airway obstruction. Our patient responded normally to the administration of isoflurane and vecuronium. Postoperatively, patients with FOP should not be extubated until fully conscious and able to ventilate adequately. Since patients with FOP are unable to walk and the ability to cough is restricted, aggressive pulmonary therapy is essential. This should include inspiratory maneuvers, chest physiotherapy and adequate hydration.

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Relationship Between Hemodynamic and Electroencephalographic Changes During General Anesthesia

Paul F. White, PhD, MD, and Walter A. Boyle, MD

Key Words: ANESTHESIA—depth. ANESTHETICS, INTRAVENOUS—propofol. MONITORING—electroencephalography (EEG), spectral edge frequency (SEF).

Anesthesiologists routinely use clinical signs to make decisions regarding the amount of anesthetic medication to administer during an operation. Difficulty in judging depth of anesthesia and concerns about awareness during "balanced anesthesia" have renewed interest in cerebral function monitors. The availability of a simple, reliable, and sensitive monitor for determining the "depth of anesthesia" would be extremely valuable in assessing the anesthetic and analgesic needs of the paralyzed patient during surgery. While anesthesiologists rely on autonomic responses (e.g., blood pressure, heart rate, diaphoresis) to decide whether or not a paralyzed patient is adequately anesthetized, the relationship between these responses and cerebral activity has not been well-characterized during an operation.

The availability of EEG monitors that process the electrical activity of the cerebral cortex have simplified the recognition and interpretation of EEG changes during anesthesia. In a recent study, Rampil and Matteo reported that the electroencephalogram (EEG) was a sensitive and convenient measure of the depth of anesthesia during induction with thiopental (1). These investigators were able to demonstrate a correlation between the EEG spectral edge frequency (SEF) and the hemodynamic responses to laryngoscopy. Others have suggested that the EEG reflects the depth of anesthesia when a barbiturate (2) or high-dose narcotic (3,4) technique is used.

In this report, the relationship between changes in hemodynamic variables, anesthetic drug concentrations and compressed EEG activity, using the Lifescan™, an acceptable alternative to the conventional 16-lead EEG for detection of cerebral ischemia during carotid endarterectomy (5), was examined in six patients anesthetized with propofol and nitrous oxide. Since previous studies have demonstrated a good correlation between blood propofol levels and emergence times from anesthesia when propofol was administered for induction and maintenance of general anesthesia (6), we evaluated the relationship between EEG changes and the rate of emergence from anesthesia.

Methods

Six consenting ASA physical status I or II adult patients undergoing elective operations were studied. The protocol was approved by the local institutional review board. These unpremedicated patients were taken to the operating room where an 18 ga iv catheter was inserted into a forearm vein. Monitoring devices included: EKG, Dinamap® blood pressure cuff, Puritan-Bennett capnograph, Nellcor® pulse oximeter, and Neurometric Lifescan™ EEG device.

The Lifescan™ performs an aperiodic analysis of the EEG signals obtained from a five-lead, dual-hemisphere, disposable electrode system. After preparing the skin with Omni Prep™ (DO Weaver, Denver, Colorado) and alcohol wipes, electrodes were placed over the frontal and mastoid areas bilaterally. In addition, a reference electrode was placed in the midline frontally. EEG signals from both hemispheres were displayed on a full-color, high resolution screen as three-dimensional parallelograms with frequency versus amplitude on the x-y axes and time on a diagonal z-axis (Fig. 1). Data for each case were

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Address correspondence and reprint requests to Dr. White, Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, MO 63110.

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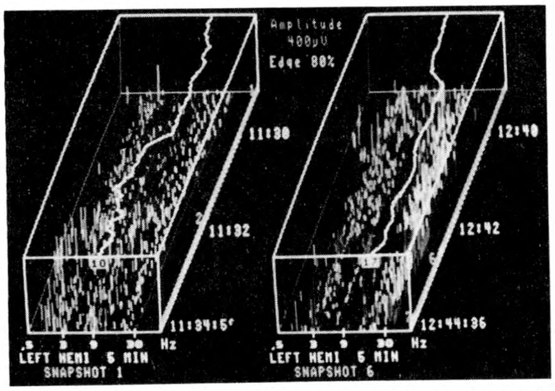

Figure 1. Photographs of the Lifescan video screen during induction (left) emergence (right) from propofol anesthesia (Patient #3). Propofol, 2 mg/kg iv, was administered at 11:32 (left) and N_2O was discontinued at 12:40 (right). Frequency is displayed on the x-axis with a non-linear scale. The amplitude of each EEG wave is a vertical "pole" and is referred to the top of the transparent box which is 400 uV. Time is displayed on the diagonal axis with the most recent time at the bottom of the parallelogram. Each display represents 5 min of EEG data.

stored in memory and were reviewed immediately after the operation. Values for mean arterial pressure (MAP), heart rate (HR), and the 80% spectral edge frequency (SEF) were recorded at 1–3 min intervals during the perioperative period.

All patients received meperidine, 1 $mg \cdot kg^{-1}$ iv, and d-tubocurare, 3 mg iv, 3–5 minutes prior to induction of anesthesia. Anesthesia was induced with propofol, 2 $mg \cdot kg^{-1}$ iv, and succinylcholine, 1.5 $mg \cdot kg^{-1}$ iv, over 30–90 seconds. After tracheal intubation, maintenance anesthesia was initiated with a propofol infusion, 10 $mg \cdot kg^{-1}$ iv, and nitrous oxide (N_2O) 67% in oxygen. Muscle relaxation was maintained with pancuronium (total dose of 4–10 mg iv) and ventilation was controlled to maintain an end-tidal carbon dioxide level of 34-38 torr. The propofol infusion rate was increased when patients showed clinical signs of inadequate anesthesia (e.g., ≥20% increases in MAP or HR, diaphoresis, lacrimation). If signs of "light" anesthesia persisted after administering two bolus injections of propofol (20–40 mg iv) and increasing the propofol maintenance infusion rate, supplemental doses of meperidine, 10–20 mg iv, were administered. Conversely, the propofol infusion rate was decreased when signs of excessive drug effect were noted (e.g., ≥20% decreases in MAP or HR). The propofol infusion was discontinued at the end of the operation and the residual neuromuscular blockade was reversed with neostigmine, 2.5–5 mg iv, and glycopyrrolate, 0.5–1.0 mg iv. After reversal of neuromuscular blockade, N_2O was discontinued and times to awakening (eye opening in response to verbal command) and orientation (to person and place) were recorded.

Peripheral venous blood samples were obtained at intervals of 10–30 minutes during and immediately after the operation from the arm contralateral to the propofol infusion. Blood samples were collected in sealed containers and stored at 5°C. Blood propofol levels were determined using an HPLC fluorescence technique, with an assay variability of 7 percent and a lower limit of detection of 0.05 µg/ml (6).

Results

Demographic data for the six study patients are summarized in Table 1. With induction of anesthesia, there was a consistent spectral shift into the low-frequency (delta) EEG range (Table 2, Fig. 1). An increase in the SEF accompanied the increase in MAP and HR following both endotracheal intubation (2–3 minutes after induction of anesthesia) and surgical stimulation in only one of the six patients studied (Fig. 2). As in patient #6 (Fig. 4), the SEF remained remarkably stable after induction of anesthesia in patients #1, #2 and #3 despite significant hemodynamic changes in response to laryngoscopy, intubation and surgical manipulations. Furthermore, while SEF decreased in response to increases in the propofol maintenance infusion rate and blood propofol levels in two cases (Figs. 2, 3), the SEF did not correlate with propofol levels or the infusion rate in other cases (Fig. 4). Finally, a predictable spectral shift into the higher EEG frequency range followed discontinuation of N_2O (Table 2, Fig. 1), and the rate of return of the SEF toward the baseline value was negatively correlated with the time to awakening after discontinuing anesthesia (Fig. 5).

Discussion

Preliminary EEG studies indicated that the functional status of the brain prior to laryngoscopy and intubation predicted the hemodynamic response to those stimuli (1,8). Although decreases in EEG-SEF were typically seen following induction of anesthesia (Table 1, Fig. 1), we failed to observe consistent changes in the EEG-SEF associated with hemodynamic responses during laryngoscopy and intubation in our patients. In contrast to the study by Rampil and Matteo (1), significant increases in blood pressure (>20% above baseline) occurred even though the SEF was below the "threshold value" of 14 Hz prior to laryngoscopy cited by Rampil and Matteo. The difference in results between our data and those reported by Rampil and Matteo may be related to the

Table 1. Demographic Data for the Six Study Patients

Patient No.	Age (yr)	Weight (kg)	Sex (M/F)	Type of operative procedure	Anesthesia time (min)	Propofol dosage (mg)	Propofol dosage (mg/min)
1	30	56	M	intra-abdominal	242	2340	9.7
2	22	61	F	intra-abdominal	141	1060	7.5
3	56	80	M	cystoscopy/TURB	68	550	8.1
4	53	90	F	intra-abdominal	155	1270	8.2
5	59	68	F	intra-abdominal	137	1800	13.1
6	51	58	M	intra-abdominal	178	1890	10.6

Table 2. Changes in EEG Spectral Edge Frequency During Induction, Maintenance, and Recovery from Propofol Anesthesia

		Spectral edge frequency (Hz)				
Patient No.	Baseline value	After induction	After intubation	Skin incision	End anesthesia	Awakening
1	18	12	13	15	12	17
2	17	7	13	14	13	16
3	19	8	9	10	10	18
4	19	10	12	15	12	19
5	16	10	10	10	9	15
6	17	10	10	11	10	16
Mean	17.7	9.5*	11.2*	12.5*	11.0*	16.8
(±S.D.)	±1.2	±1.8	±1.7	±2.4	±1.5	±1.5

*Significantly different from the baseline value, $P < 0.05$.

fact that different induction agents (i.e., propofol versus thiopental) were used. Alternatively, this previously reported "threshold value" may only be valid for monitors using the same algorithm for analyzing the EEG signal. Interestingly, our baseline (pre-induction) and post-induction (pre-laryngoscopy) SEF values (Table 2) were remarkably similar to those reported by Rampil and Matteo.

The lack of a simple and reliable brain monitor for determining awareness during nitrous-narcotic-relaxant anesthesia has raised concerns about the increasing clinical popularity of brain monitors during anesthesia (9). Given the poor correlation between a commonly accepted clinical sign of anesthetic depth (i.e., hemodynamic responsiveness to surgical stimuli) and the EEG-SEF, many anesthesiologists would question the value of using the EEG to assess depth of anesthesia during an operation.

One explanation for the lack of correlation between changes in the cardiovascular variables and the EEG-SEF in our study may be that the sensitivity of the Lifescan EEG monitor is limited at the 80% SEF. Alternatively, our findings may reflect the fact that the EEG-SEF was above the "threshold" required for propofol to suppress hemodynamic responses to painful stimuli. In one case (Fig. 3, event #6), how-

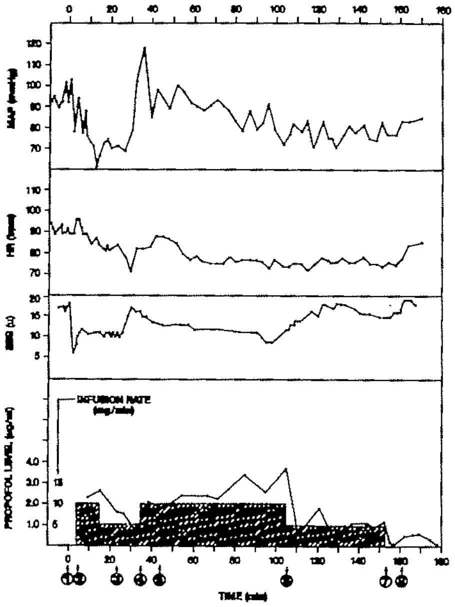

Figure 2. Relationship between hemodynamic changes, EEG spectral edge frequency, propofol infusion rate (hatched area), and blood propofol levels during the perioperative period in patient #4. The numbers on the abscissa correspond to the following events: 1 propofol induction, 2 mg·kg^{-1} iv; 2 propofol infusion, 10 mg·kg^{-1} iv; 3 skin incision; 4 opening of abdominal cavity; 5 intra-abdominal manipulation; 6 excision of surgical specimen; 7 discontinuation of N_2O; and 8 awakening.

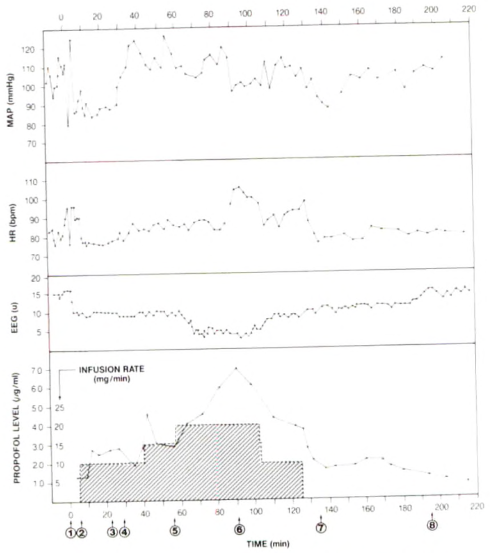

Figure 3. Relationship between hemodynamic changes, EEG spectral edge frequency, propofol infusion rate (hatched area), and propofol blood levels during the perioperative period in patient #5. The numbers on the abscissa correspond to the following events: 1 propofol induction, 2 mg·kg^{-1} iv; 2 propofol infusion, 10 mg·kg^{-1} iv; 3 skin incision; 4 opening of abdominal cavity; 5 intra-abdominal manipulation; 6 excision of surgical specimen; 7 discontinuation of N_2O; and 8 awakening.

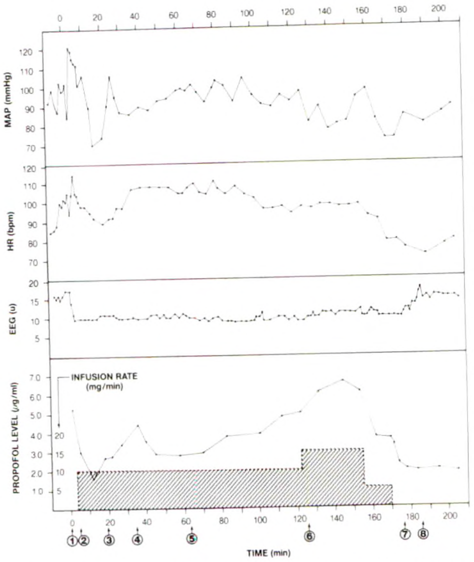

Figure 4. Relationship between hemodynamic changes, EEG spectral edge frequency, propofol infusion rate (hatched area), and blood propofol levels during the perioperative period in patient #6. The numbers on the abscissa correspond to the following events: 1 propofol induction, 2 mg·kg^{-1} iv; 2 propofol infusion, 10 mg·kg^{-1} iv; 3 skin incision; 4 opening of abdominal cavity; 5 intra-abdominal manipulation; 6 excision of surgical specimen; 7 discontinuation of N_2O; and 8 awakening.

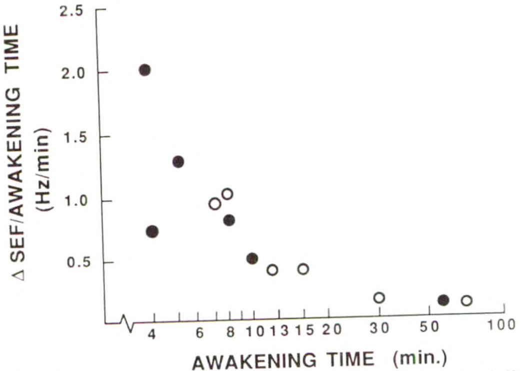

Figure 5. Relationship between the time to awakening [following discontinuation of nitrous oxide (○) or propofol infusion (●)] and change in the EEG spectral edge frequency (SEF).

ever, significant tachycardia developed in spite of a high propofol infusion rate (20 mg/min) and a low EEG-SEF (<5 Hz). In addition, the low EEG-SEF activity at the time of the episode was associated with a high blood propofol concentration. Although administration of small supplemental doses of meperidine was effective in decreasing the MAP and HR responses during surgery, there were no obvious changes in the EEG-SEF recording after meperidine administration (unreported data). The lack of correlation between the EEG-SEF and autonomic responses to surgical stimuli may have occurred because hemodynamic responsiveness is not an appropriate gauge of anesthetic depth under these (surgical) conditions.

It is possible that autonomic (hemodynamic) responses to surgical stimuli are more closely related to neurophysiologic events in either the brainstem or spinal cord than to cortical events, which would more likely be reflected in the EEG-SEF. The Lifescan EEG recording technique may not have been sufficiently sensitive to detect these transient changes in central nervous system activity. Furthermore, our findings may be related to the specific anesthetic technique and might not apply when the EEG is used to monitor depth of anesthesia with other anesthetic or analgesic drugs.

If the goal of general anesthesia is "to render the patient unconscious, thereby preventing pain, anxiety and recall of intraoperative events" (10), one might question the appropriateness of using hemodynamic responses to determine the anesthetic and/or analgesic needs of anesthetized patients. The old dictum that, if the patient moves or has increased cardiovascular responsiveness to a surgical stimulus, "give more anesthesia" may have to be revised. For example, when a patient shows hyperdynamic cardiovascular responses in the presence of stable but depressed EEG activity, perhaps consideration should be given to suppressing the autonomic responses with either centrally (e.g., alpha$_2$-agonist drugs) or peripherally (e.g., β-blockers, vasodilator drugs) active sympatholytic drugs.

As reported previously (11), discontinuation of nitrous oxide was associated in our patients with a significant increase in EEG activity, and there appeared to be a negative correlation between changes in the EEG-SEF and times to awakening and orientation after anesthesia (Fig. 5). In agreement with the findings of other investigators (1,2,12,13), our data indicate that the EEG appears to be capable of monitoring anesthetic drug effects on the central nervous system in the *absence* of surgical stimulation. For example, Schwilden et al. have described a closed-loop feedback control system for monitoring methohexital's hypnotic effect in volunteers using a quantitative EEG analysis (12). These investigators also described the use of a pharmacokinetic-dynamic EEG model for quantitating the effects of propofol on the central nervous system in volunteers (13).

When propofol administration was monitored with a cerebral function monitor (14), "easily recognizable" EEG patterns were reported to be associated with increasing depth of anesthesia. Although there was marked interpatient variation, there was good correlation between propofol blood levels and EEG changes recorded by a cerebral function monitor (14). Recently, Stanski and colleagues suggested that during alfentanil-nitrous oxide anesthesia the EEG-SEF could be used to indicate an inadequate depth of surgical anesthesia (15). However, significant variability was noted in the individual patient responses.

We found no consistent relationship between hemodynamic responsiveness to surgical stimulation and changes in EEG spectral edge frequency during general anesthesia with propofol and nitrous oxide. Marked increases in MAP and HR occurred without concomitant changes in the EEG-SEF. Further studies are needed to define the relationship between cerebral and hemodynamic responses to specific surgical stimuli using a variety of general anesthetic techniques.

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Prognostic Significance of Reperfusion Hyperglycemia during Liver Transplantation

Susan V. Mallett, FFARCS, Yoogoo Kang, MD, Judith A. Freeman, MD, Shushma Aggarwal, MD, Thomas Gasior, MD, and Frank L. Fortunato, MD

Key Words: ANESTHESIA—liver transplantation. LIVER—transplantation. SURGERY, TRANSPLANTATION—liver.

The liver occupies a central role in carbohydrate metabolism and glucose homeostasis. Consequently, significant changes in blood glucose level can be anticipated in patients with end-stage liver disease undergoing orthotopic liver transplantation (OLT) (1). Contrary to earlier reports (2), hypoglycemia during OLT has proven to be an uncommon problem: blood glucose levels generally remain within the range of 100–200 mg% even without dextrose infusion, owing to the administration of glucose in blood anticoagulated with citrate-phosphate-dextrose-adenine (CPDA-1), together with decreased glucose utilization secondary to anesthesia and inadvertent hypothermia (3). Hyperglycemia, however, is a consistent finding after reperfusion of the grafted liver. Blood glucose levels increase rapidly on reperfusion, slowly decreasing without treatment toward the end of the procedure (4). Postreperfusion hyperglycemia has also been seen in an animal model, and may be the result of a massive release of glucose from the donor liver presumed secondary to ischemic injury to the donor liver, which allows intracellular glucose to leak out of the hepatocytes (5). Therefore, the degree of hyperglycemia in the neohepatic stage may be a reflection of the ischemic insult sustained by the grafted liver. To determine the relation between the degree of reperfusion hyperglycemia and the functional recovery of the grafted liver, intraoperative glucose levels and subsequent liver function in adult patients undergoing OLT were studied retrospectively.

Methods

The records of 90 consecutive adult patients (range 19–64 years) undergoing orthotopic liver transplant (OLT) were reviewed. Anesthesia was induced with ketamine or thiopental and maintained with fentanyl, isoflurane, and pancuronium. The only source of exogenous glucose was that transfused in CPDA-1 blood; glucose-free crystalloid solution was used (Plasma-Lyte A, Travenol Laboratories Inc.). In the few instances when blood glucose decreased below 80 mg%, however, a 5% dextrose solution was administered. Blood products were administered via a rapid-infusion system in a ratio of red blood cells, 300 ml:fresh frozen plasma, 200 ml:Plasma-lyte, 250 ml to maintain intravascular volume, and glucose concentration of the mixture was 150–250 mg%. Platelets and cryoprecipitate were also transfused as indicated. A veno-venous bypass was used in all patients, and methylprednisolone (1 g) was given IV for immunosuppression within 5 min of reperfusion. Arterial blood glucose levels were measured hourly, as well as more frequently during the anhepatic stage and immediately after reperfusion, using a glucose oxidase test (YSI model 23 A glucose analyzer, Yellow Springs Instruments).

Patients were classified into two groups according to the postoperative outcome of the grafted liver: patients in group 1 had relatively adequate hepatic function for the first 3 postoperative days, whereas group 2 patients had grossly inadequate hepatic function and required retransplantation within 3 days. Intraoperative blood glucose levels in patients in group 2 were compared with those in group 1.

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Address correspondence to Dr. Kang, Department of Anesthesiology, Presbyterian-University Hospital, DeSoto at O'Hara Streets, Pittsburgh, PA 15213.

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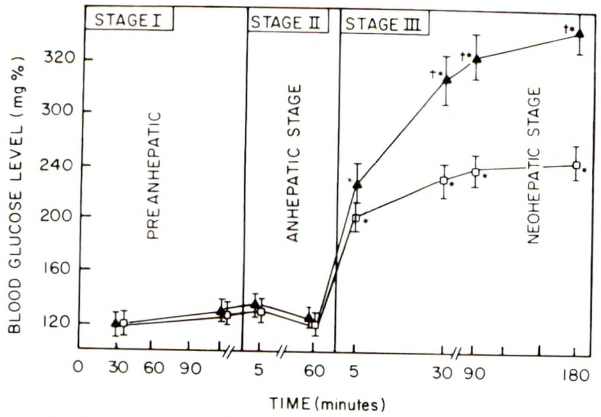

Figure 1. Blood glucose levels during liver transplantation. $*P < 0.05$ compared with the baseline value. $†P < 0.01$ compared with the corresponding values of group 1 patients. (□), Group 1 ($n = 7$): patients who had adequate liver function postoperatively. (▲), Group 2 ($n = 13$): patients with nonfunctional livers who required retransplantation.

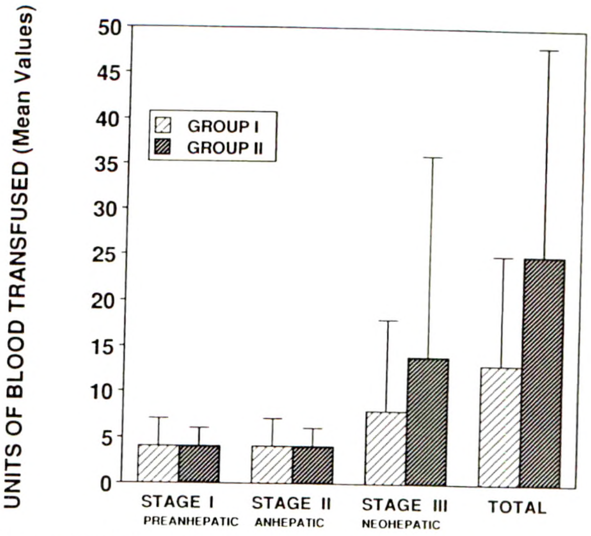

Figure 2. Units of blood transfused (mean and SD).

Analysis of variance of repeated measures and linear correlation were used for statistical analysis; $P < 0.05$ was considered statistically significant.

Results

Of the 90 patients, 77 met the criterion for inclusion in group 1 and 13 in group 2. The patients in group 2 were categorized by the surgical team as having primary nonfunctional grafts (PNFG).

Blood glucose levels during OLT are shown in Figure 1. Mean blood glucose levels ranged from 100 to 200 mg% during the preanhepatic and the anhepatic stages and were similar in both groups of patients. Ten patients had blood sugar levels below 100 mg% during the anhepatic stage; three of these patients (blood sugar <80 mg%) required a glucose infusion to increase the blood sugar to an acceptable level.

In all patients blood glucose levels increased abruptly at 5 minutes postreperfusion; the increase was similar in the two groups of patients (202 ± 35 mg% in group 1; 225 ± 43 mg% in group 2). In group 2, however, blood glucose levels continued to increase and were significantly higher than those in group 1 at 30, 90, and 180 minutes after reperfusion.

Blood transfusion requirements (Fig. 2) were similar in the two groups of patients during the preanhepatic and anhepatic stages (4 ± 3 [SD] and 4 ± 2 units in group 1, and 4 ± 2 and 4 ± 2 units in group 2, respectively). Patients in group 2, however, required more blood transfusions after reperfusion of the grafted liver (14 ± 22 units compared with 8 ± 10 units in group 1). No statistical correlation was found between the amount of blood transfused during the neohepatic stage and the blood glucose levels in the two groups of patients (Fig. 3).

Discussion

Under normal circumstances, the liver is both the sole site of glucose production, from either glycogenolysis or gluconeogenesis, as well as a major site of glucose consumption and disposal. Liver disease, therefore, can interfere with glucose metabolism, causing glucose intolerance in cirrhotics and hypoglycemia in patients with severe hepatocellular damage (6–8). This abnormal glucose metabolism can be further complicated during OLT, a procedure that encompasses the preanhepatic stage, with marginal hepatic function; the anhepatic stage, with no hepatic function; and the neohepatic stage, when the grafted liver recovers from ischemic injury. Nevertheless, relatively normal blood glucose levels are seen during the preanhepatic and anhepatic stages of surgery, owing to blood transfusion.

By contrast, an abrupt increase in blood glucose level occurs on reperfusion. This sudden increase is thought to be due to massive release of glucose from the grafted liver, as evidenced by very high glucose levels in hepatic venous blood compared with relatively low arterial levels (5,9). Glucose is stored as glycogen in the liver, and glycogenolysis is normally an energy-consuming process, but glycogenolysis is known to occur in the hypothermic condition owing to the hepatic release of α-glucosidase (10). Changes in cell membrane permeability as a consequence of

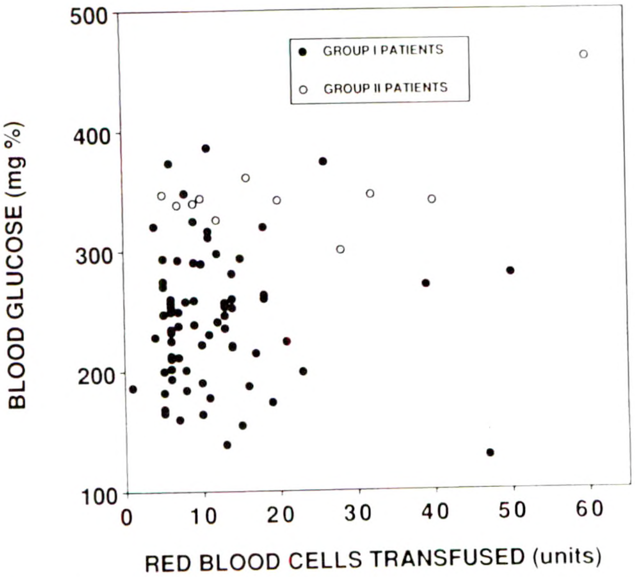

Figure 3. Correlation between blood glucose level (120 min after reperfusion) and total volume of red blood cells transfused ($r_2 = 0$).

ischemic damage may then allow leakage of intracellular glucose into the extracellular fluid.

The patients who required early retransplantation as a result of poor graft function (group 2) showed much more severe and persistent hyperglycemia. Lampe et al. (11) demonstrated that previous ischemia influences the capacity of the liver to recover its glycogen content when normal circulation is reestablished, and that the degree of subsequent glucose intolerance correlated strongly with the magnitude of the ischemic insult. Therefore, the persistent reperfusion hyperglycemia in group 2 patients may be related to reduced glucose uptake and also to potential continued glycogenolysis as a result of postreperfusion warm ischemic damage.

Other factors may influence blood glucose levels, but their effects do not appear to have played a role in our subjects. Stress effects of anesthesia and surgery were similar in all patients, as there was no difference in cardiovascular stability in the two groups (12). All patients received identical doses of methylprednisolone (13). Although patients in group 2 received more blood than did those in group 1, no statistical correlation was found between the amount blood transfused and the blood glucose level. Furthermore, some patients in group 2 had progressive hyperglycemia, irrespective of blood transfusion, whereas some patients in group 1 who received large transfusions had glucose levels that did not exceed 280 mg%. The overall increased requirements for blood in the neohepatic stage in group 2 patients is not surprising, because more severe coagulopathy is associated with impaired hepatic function (14). The Collins preservation solution (glucose 3.75%) may contribute to the early increase in blood glucose levels. Because of rapid distribution, however, its effect must be transient. Also, reperfusion hyperglycemia was seen even with grafts preserved in glucose-free solution (15). Glucagon levels are known to increase after reperfusion in an animal model (5), but their role in human liver transplantation is still unclear.

Investigation of more long-term glucose metabolism could have been desirable. However, postoperative blood glucose level was not analyzed because of a vast difference seen in postoperative course. Although reperfusion hyperglycemia was seen in most patients, its clinical significance in metabolism requires further investigation.

In conclusion, the results of this study suggest that acute hyperglycemia on reperfusion of the grafted liver is most likely due to the release of glucose from ischemic hepatocytes together with hormonal changes. Persistent reperfusion hyperglycemia (>300 mg%) may be caused by impaired glucose uptake and/or continued glycogenolysis and may be an early prognostic indicator of impaired graft function.

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Fifty-five Years Ago In Anesthesia & Analgesia

E. A. Rovenstine: A Method of Combining Anesthetic and Surgical Records for Statistical Purposes. Anesthesia and Analgesia: 1934;13:122–128.

Rovenstine wrote this article while still in Ralph Waters' department of anesthesia at the University of Wisconsin in Madison before moving upward and onward to fame and glory as the head of anesthesia at Bellevue Hospital in New York City. This paper represents the earliest approach to the systematic tabulation of data relating to anesthetic techniques, agents and complications in numbers large enough to allow statistically valid epidemiologic studies to be carried out. The author clearly defines the need for compilation of such data in the opening sentence: "Statistical reports relating to anesthesia have been noticeably barren of convincing evidence". True enough in 1934—any less true 55 years later? In any event, Rovenstine addresses the problem of obtaining data adequate to provide convincing evidence to support or refute popular clinical impressions by introducing and describing a system based upon the use of rectangular cardboard cards, about 9 × 3-3/4 inches (22.5 × 9.4 cm). Data from standardized anesthesia records with spaces to record details of intra-operative data on one side and pre- and postoperative data on the other side, in itself an innovation, were transferred to the cards by using a conductor's punch to punch out appropriate numbers in 45 vertical columns and 10 horizontal rows. The numbers in the vertical columns included spaces for data on anesthetist, surgeon, operation, pre-medication, anesthetic agent(s) and technique, duration of anesthesia, pre- and postoperative data, etc. A large code card defined what the numbers represented and gave instructions on how to enter data. Hundreds of the completed cards could be sorted and analyzed in a relatively short time by using a tabulating and sorting machine rented from (who else?) the International Business Machines Corp. (We also found, in the absence of the IBM sorter, that cards of this type could be sorted for analysis, albeit more slowly, by skillful manipulation of a darning needle through the punched out holes.) The technique that Rovenstine described was subsequently widely used throughout North America. It had major limitations and disadvantages, but at least it was a step forward in meeting the challenge of getting hard data to prove or disprove *scientifically* the validity and rationale of clinical practice, a challenge we still face.

Letters to the Editor

Further Evidence that Analgesia and Anesthesia Are Mediated by Differing Mechanisms

To the Editor:

The importance of making a clear distinction between the phenomena of analgesia and anesthesia in relation to opioid action (1) has been brought into sharp focus by the recently published work of Stone and DiFazio (2). They have presented evidence of the possibility that the anesthetic effects of opiates/opioids may be mediated by a membrane effect in addition to the well established receptor interaction. This supports the contention that analgesia and anesthesia are mediated by different mechanism (3,4). The state of anesthesia may require only a non-specific membrane lipid effect, whilst opioid analgesia requires only a specific receptor action at opioid receptors. This concept is supported by the finding that the loss of righting reflexes in animals produced by an opioid can be antagonized by pressure (5). This concept cannot preclude a further possibility; that opioid anesthesia might require concurrent opioid receptor occupation as well as a non-specific membrane effect. Previously, I have suggested that the apparently contradictory findings regarding the effects of opioid antagonists on nitrous oxide analgesia have largely been caused by investigators not clearly distinguishing studies involving analgesia from those involving anesthesia (4). If this distinction is made it is clear that opioid antagonists do reverse the analgesic effects of nitrous oxide. Thus the work alluded to above adds further support to the contention that analgesia and anesthesia are mediated by different mechanisms and that nitrous oxide has opioid effects.

M. A. Gillman, MD
South African Brain Research Institute
Suite 9 Highlands House (NBS Centre)
173 Louis Botha Avenue
Orange Grove 2192
Johannesburg, South Africa

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Is Magnesium Sulfate an Anesthetic?

To the Editor:

Thompson et al. (1) studied the possible effects of $MgSO_4$ on the MAC of anesthetised rats, using the tail-clamp technique. At plasma Mg^{++} levels of 15.8 ± 1.57 mg/dl they reported the MAC of halothane was reduced to 61.6% of control.

Pritchard et al. (2) reported that the therapeutic levels of Mg^{++} to treat preeclampsia to range from 4 to 6 mg/dl (2). The authors admitted that plasma Mg^{++} levels of 15 mg/dl or more are accompanied by respiratory depression, abolishment of deep tendor reflexes and many other signs of striated muscle weakness (3,4). In the study by Somjen et al. (4), the two subjects (authors) gave each other enough $MgSO_4$ to produce respiratory depression and cyanosis; the third author, Stephen, ventilated both to full recovery. Both subjects felt and heard everything happening upto when the Mg^{++} levels exceeded 14 mEq/l. No signs of anesthesia were noted, but the hand grip force was markedly reduced. Peck and Melzer (5) reported in three patients undergoing herniorrhaphy under attempted $MgSO_4$ infusion anesthesia that the anesthetic conditions in all three cases were disastrous, two of the three even needing resuscitation.

Though both magnesium and ritodrine are tocolytic agents, the conclusion that the former has anesthetic properties without having monitored the neuromuscular junction activity is comparable to assuming that under the condition of the author's experiments (1), d-tubocurine potentiates halothane's MAC.

We agree that patients receiving $MgSO_4$ therapy frequently present a special challenge to the anesthesiologist. However, we are also aware that the effect of $MgSO_4$ is mostly limited to peripheral nerve, skeletal conductive muscle, and the cardiovascular system. The suppression of myocardial conduction and contractility, leading to a decrease in peripheral resistance and cardic output is well known. The effects of magnesium on the CNS are relatively minor (6). Although Thompson et al. found their rats

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moving after the discontinuation of halothane, while still receiving $MgSO_4$ infusion, in order to substantiate their claim that marked anesthetic effect coincided with increased levels of $MgSO_4^{++}$ would have required continuous monitoring of neuromuscular activity. Reserpine and methyldopa decrease MAC, but they are not considered anesthetics. If, in addition to producing muscle relaxation, $MgSO_4$ depletes CNS monoamines or suppresses the sympathetic nervous system, one might then accept that anesthetic requirements are lowered by $MgSO_4$. Thus far, the evidence sufficient to characterize $MgSO_4$ as an anesthetic is not available.

J. Antonio Aldrete, MD, MS
Department of Anesthesiology & Critical Care
Cook County Hospital
1835 W. Harrison St.
Chicago, IL 60612

Afzal Vazeery, MD, PhD
Department of Anesthesiology & Critical Care
Cook County Hospital
1835 W. Harrison St.
Chicago, IL 60612

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In Response:

The letter by Aldrete and Vazeery makes one important point and that is that in carrying out any study evaluating anesthetic efforts, the results must not be clouded by the concomitant presence of neuromuscular paralysis. This point was carefully considered in the experimental design of our study that Aldrete and Vazeery are commenting upon, and safeguards were built into the experiment to exclude this possibility. These were: 1) The Mg^{++} infusion remained constant throughout each experiment, both during anesthetic exposure and after the anesthetic was discontinued; 2) MAC, as customarily carried out, was determined as the point midway between an anesthetic concentration that produced no movement and one that produced gross movement to a tail clamp stimulus. This result was usually achieved with 0.1% decrement in halothane concentration. Gross movement occurred in all animals thus evaluated with a minimal change in anesthetic concentration; 3) Animals at the end of the experiment and with continued constant Mg^{++} infusion moved freely and without evidence of paralysis; 4) Physiologic parameters of heart rate and arterial blood pressure were continuously monitored (It is of interest to note that heart rate and blood pressure did not increase with a negative response but did increase with a positive response to a stimulus); 5) Arterial blood gas tensions were controlled and hypoxia was carefully excluded and thus made no contribution to anesthetic evaluation. Therefore, it remains our opinion that the study as carried out does correctly reflect the anesthetic effect of increasing plasma Mg^{++} concentration. This article points out the clinical range commonly used by obstetricians and also points out the clinical guide using reflex responses with a loss of reflex response occurring above 10 mg/dl. In an institution where the use of Mg^{++} for pre-eclampia is widespread (obstetricians at the University of Virginia are the cornerstone of Mg^{++} infusion studies), occasional patients do have a loss of deep tendon reflexes and infusions are curtailed. In no instance have any of these patients been paralyzed.

In addition, the contribution of this article is to make anesthesiologists aware that Mg^{++} can make an anesthetic contribution; however, Mg^{++} is not to be considered a complete anesthetic. In fact, at a plasma concentration that should never be exceeded, a maximal anesthetic contribution of less than 40% of the total anesthetic requirement was achieved. That is hardly a complete anesethetic; however, it needs to be carefully considered when assessing anesthetic needs.

In conclusion, this article contributes the first real study of the anesthetic effectiveness of Mg^{++} in contrast to the previously uncontrolled reports and anecdotal comments available.

Stephen W. Thompson, MD
Jeffrey C. Moscicki, MS
Cosmo A. DiFazio, MD, PhD
Department of Anesthesiology
University of Virginia Medical Center
Charlottesville, Virginia 22908

Epidural Fentanyl As a Test Dose

To the Editor:

We would like to report on a potential benefit from the addition of a narcotic to epidural analgesia that we have not seen reported in the literature as a indicator of accidental intravascular injection.

A healthy 28-year-old primagravida in labor requested epidural analgesia. With the patient in the sitting position, a 17 gauge Weiss epidural needle was placed into the epidural space at the L 2-3 interspace with the loss of resistance to air technique. After confirming the absence of cerebrospinal fluid or blood return upon aspiration, a test dose of 3 ml bupivacaine, 0.25 percent without epinephrine was injected through the needle. A epidural catheter was then passed through the needle without difficulty, the needle withdrawn, and the catheter secured. Following attempted aspiration of cerebrospinal fluid or blood from the catheter, a second, identical test dose was injected. There were no central nervous system symptoms reported by the patient, though solicited. The patient was placed then into the supine position with left uterine displacement. Aspiration through the catheter was again negative. A third dose of anesthetic consisting of bupivacaine .25 percent plus fentanyl 100 μg was injected. Within thirty seconds the patient stated that she was feeling "spacy". She denied tinitus or dysgeusia. Maternal vital signs and fetal heart rate were unchanged. Accidental intravascular injection was suspected. Aspiration through the catheter was yet again unsuccessful. The patient was awake but sedated. She reported a lessening of the pain of her contractions. She had no motor block. An additional test dose of 3 ml of lidocaine 1.5 percent with 15 μgm of epinephrine was injected with a prompt and transient increase in maternal heart rate from 60 to 86 beats per minute.

The epidural catheter was withdrawn with continued aspiration through it that was, for the first time, positive for blood. The patient was given a second, uneventful epidural without additional narcotic. She had good analgesia for the remainder of her labor. A female infant with 1 and 5 minute Apgar scores of 9 and 9 was delivered one hour and fifty minutes following the accidental intravascular injection.

We believe that the fentanyl injected was responsible for the patient's sudden sedation and altered pain perception, a response that alerted us to the intravascular placement of the catheter. We do not suggest that this constitutes a reason for the use of epidural fentanyl, only that if fentanyl is used it may offer additional symptoms, and possibly signs (e.g. miosis, bradycardia) that might alert one to intravascular placement of an epidural catheter.

Andrew B. Freeman, MD
Linda Hicks, CRNA
Medical City Hospital
Suite A-310
7777 Forest Lane
Dallas, Texas 75230

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Book Reviews

Local Anesthetics

G. A. Strichartz, Ed., New York, Springer-Verlag, 1987, 292 pp, $169.00.

This is Volume 81 in the Handbook of Experimental Pharmacology. It should have been reviewed earlier. Better late than never, however, especially for material like this, given the touch of timelessness that it has. In 284 closely written pages of text the pharmacology of local anesthetics at the basic science, molecular mechanism level is reviewed and discussed to an extent this reviewer has never before encountered. This is done in exquisite detail but with such consistent clarity that even this naive reader was able to follow, understand and appreciate complex concepts that turned out to be not nearly as arcane as they were thought to be before starting to read about them in this book. Descriptions of molecular mechanisms are blessedly leavened, however, with dollops of attention to the clinical relevance of some pretty complex pharmacologic principles. Edited by Strichartz, well known for his studies of the mode of action of local anesthetics, each of the eight chapters is authored by writers skilled in the art of writing clearly and with style. Eight of the 12 authors come from Harvard's Department of Anesthesia at the Brigham and Women's Hospital in Boston, the director of which is Dr. Benjamin Covino, also one of the authors. There is, however, nothing parochial about this book.

The first chapter, by Leroy Vandam, provides a complete review of and, in several ways, new approaches to the history of local anesthetics. The emphasis is, as it should be in a book like this, on the history of local anesthetics (e.g., structure and synthesis, toxicity, mode of action, pharmacokinetics), not on local anesthetic techniques.

Next comes a 31-page chapter on modern concepts of where and how local anesthetics work, all in micromolecular terms. Authored by Strichartz and, from Yale, Dr. Murdock Ritchie, a long and productive laborer in this vineyard, this chapter is a classic. In belying the overly simplistic concepts of many of us clinicians, the material in this chapter establishes a rational foundation for understanding by all of us as to how local anesthetics block axonal conduction and thus produce local anesthesia. The reader comes away from this chapter realizing, first, that the anesthetic action of any particular local anesthetic is not explicable solely on the basis of any single action of the anesthetic molecule. Cationic forms of clinically useful local anesthetics acting within the cytoplasm combine with receptors in cell membrane sodium channels to prevent movement of sodium ions through the membrane and thus prevent repolarization of the membrane. This may be the primary way they act, but local anesthetics also have other actions at other sites and they, too, contribute in variable degrees to state of anesthesia. Second, not all local anesthetics act on the sodium channel receptor and at other membrane sites in the same way. This results in differences in the clinical pharmacology of local anesthetics of importance to the practising anesthesiologist. Third, even the experts differ in their concepts about how local anesthetics act. Some view mode of action in mainly mechanistic or physical terms. Others are more biologically oriented.

The third chapter (by Courtney and Strichartz) considers structural elements that determine local anesthetic activity, while the fourth chapter (by Raymond and Gissen) deals with a matter of special clinical interest: differential nerve block. Yes, pharmacologically demonstrable differential sensitivity of nerve fibers to local anesthetics does exist. It comes in two forms. One is in the unsteady state seen particularly under clinical conditions. Differential nerve block of this type is closely related to pharmacokinetics and pharmacodynamics at the tissue level. Unsteady state differential nerve block is most evident during onset and offset of regional anesthesia. The second form of differential nerve block is seen under in vitro steady state conditions impossible to duplicate in vivo. Under steady state conditions the effects of local anesthetics on isolated simple axons can be studied. In both in vivo unsteady clinical states and in vitro laboratory steady states the frequency of axonal traffic contributes an important frequency-dependent determinant of sensitivity of nerve fibers to local anesthetics. Differential nerve block and factors involved in it are of special significance in management of both acute (postoperative) pain and chronic pain, as well as in the effective use of regional anesthesics in surgery and obstetrics.

The next two chapters deal with pharmacokinetics (by Arthur) and toxicity and systemic actions of local anesthetics (by Covino). These are followed by examination by Gintant and Hoffman of the role of local anesthetic effects in the actions of antiarrhythmic drugs. This chapter will be of special interest to cardiologists and to such cardiovascular surgeons as may have a pharmacologic bent. This chapter also serves to remind anesthesiologists of the multiplicity of

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actions of local anesthetics and how they act when we use them intra-operatively to correct arrhythmias.

The final chapter (by Garfield and Gugino) on central nervous system effects of local anesthetics is a pharmacologically lucid and clinically useful review of these important side effects of local anesthetics. This chapter constitutes a fitting denouement to a complex but fascinating tale of what really happens when we use a local anesthetic.

Ideally every anesthesiologist should own this volume. This is, alas, unrealistic: the price is $169 (yes, per volume!). More realistically, this volume should be in every anesthesiologist's departmental or institutional library, available for what should be mandatory reading.

Nicholas M. Greene, MD
Professor of Anesthesiology Emeritus
Yale University School of Medicine
New Haven, CT 06510

Safety and Cost Containment in Anesthesia

J. S. Gravenstein and James F. Holzer, Editors, Boston, Butterworths, 1988, 257 pp, $22.95.

This 250 page paperback publication, which is both fascinating and enlightening, contains a series of papers written by anesthesiologists, attorneys, manufacturers, insurance experts and risk managers who met in a workshop to examine the questions of safety in anesthesia and cost containment. This workshop, held in the spring of 1987, although inspired by an economist with one of the anesthesia manufacturing companies, is also a resultant "spin-off" of the recently created Anesthesia Patient Safety Foundation.

In the preface, the editors briefly describe the history of the background workshop and then divide the book into five portions: The Nature of Risk in Anesthesia, Financial and Related Impacts of Anesthesia Mishap, Improving Anesthesia Safety Today and in the Future, Financial Decision Making with Respect to Improving Anesthesia Safety and Current Issues that Affect Safety and Cost. Since the twenty-five authors write with different degrees of talent on an interesting variety of subjects, the book does not become tiresome. Some of the articles provide an insight into the practice of anesthesiology that is different from our own viewpoint, thus providing a glimpse of how others see us and our practices.

Particularly timely are several chapters relating to risk management. Since anesthesiologists practice in settings that are susceptible to regulation (eg. the Joint Commission on Accreditation of Healthcare Organizations), these chapters are particularly pertinent. There are excellent chapters on the Tort Liability System: Overview for the Anesthesiologists and How Large, Not-for-profit Teaching Hospitals Make Decisions About Capital Expenditures. Additional chapters discuss current and new monitoring devices, all designed to improve safety to patients. Various views relating to the financial impact of these safety measures are brought into focus. The book concludes with some philosophic comments regarding the overall topic of safety and cost containment in anesthesia.

This book is timely and particularly important for all administrators or chiefs of departments of anesthesia. For the many practicing anesthesiologists that have interests in our medical-legal issues, insurance costs and hospital interactions, they will enjoy and appreciate this novel compilation.

G. W. N. Eggers, Jr., MD
Professor and Chairman
Department of Anesthesiology
University of Missouri-Columbia
Vice-President of Scientific Affairs
American Society of Anesthesiologists

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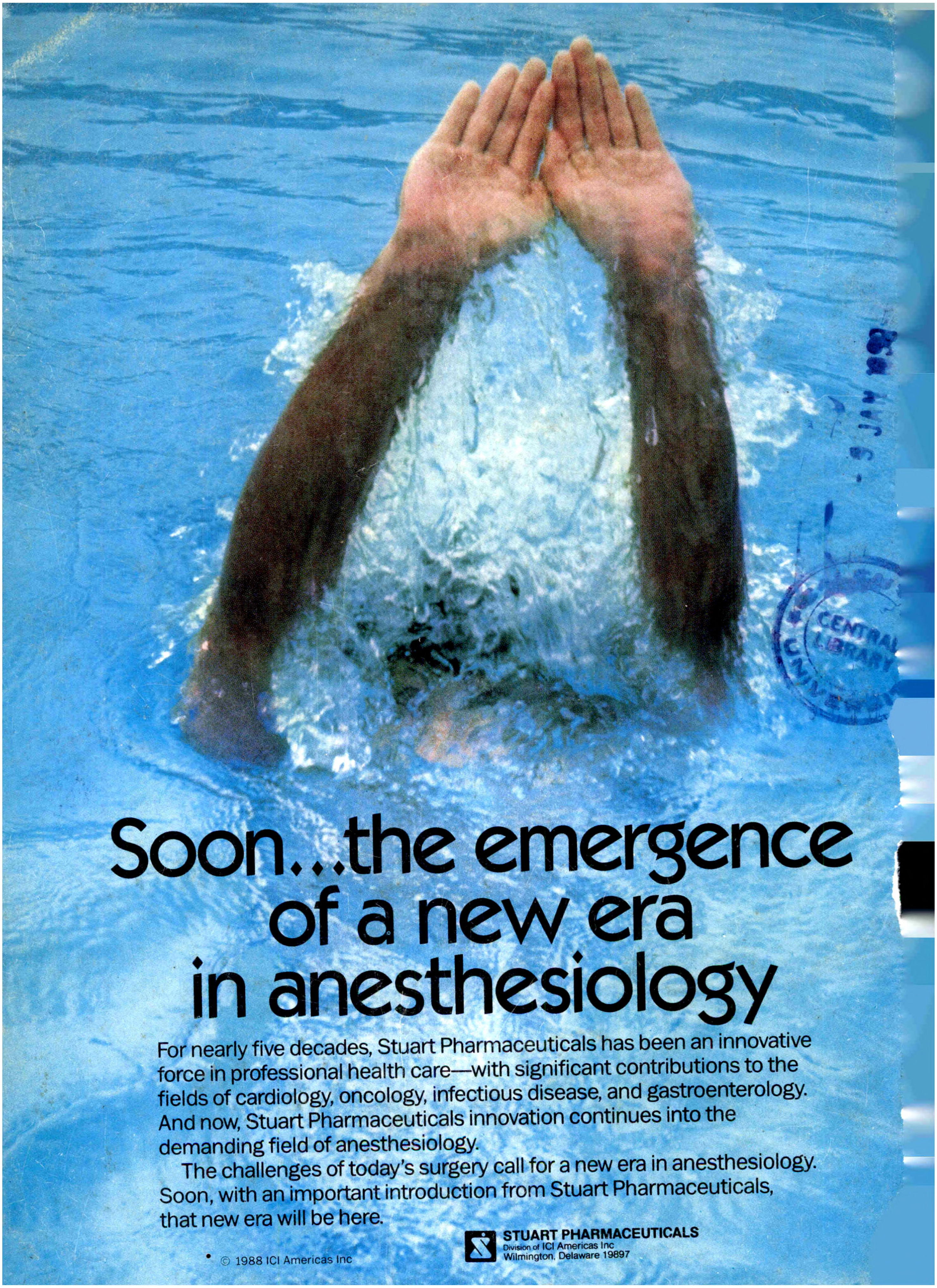
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